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Review Article

RECENT PATENTS ON SOLID DISPERSIONS OF ANTIHYPERLIPIDEMIC DRUGS

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ABSTRACT

Hyperlipidemia is a worsening health condition in developed and developing countries, especially among the younger generation due to their lifestyle. The World Health Organization reported 2.6 million deaths globally due to hyperlipidemia. Therefore, there is a huge demand of antihyperlipidemic drugs in the pharmaceutical market. Approximately 60% of the total active drug content used in hyperlipidemia suffer from poor water solubility, particularly BCS class II drugs. Poor water solubility may result in insufficient absorption and finally affects the bioavailability of the drug causes ineffectiveness in lowering lipid profile of patients. In recent years, solid dispersion technology has proved to be a simple, effective and economical approach for industrial application to increase the solubility of these drugs. This review paper is an attempt to compile up various research as well as patents reports related to solid dispersions of poor water soluble antihyperlipidemic drugs.

Keywords: Solid Dispersions, Patents, Antihyperlipidemic drugs

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INTRODUCTION

Hyperlipidemia is a major concern now a days because of a change in the people's lifestyle in developing and developed countries around the world. Global Health Observatory Data from the "World Health Organization" showed that high cholesterol level accounted for nearly one–third of Ischaemic Heart Disease and cause 4.5% (2.6 million) deaths along with 2.0% (29.7 million) disability-adjusted life years (DALYS) globally [1]. In 2007, a survey conducted on 43,368 people in China showed that individuals over the age of 18 were found to be 33% more likely to have hyperlipidemia [2]. Similarly, in 2008 the World Health Organization reported that 39% of the total adult population was suffering from high cholesterol levels [1]. Furthermore, a triennial report (2013-2016) published by the United States "Center for Disease Prevention and Control", showed that 11.8% of adults aged 20 y and older had high serum total cholesterol levels of 240 mg/dl [3]. Hyperlipidemia is a lipoprotein metabolism disorder related to elevated plasma concentration of cholesterol and triacylglycerols [4]. Hyperlipidemia is generally managed through antihyperlipidemic drugs such as statins and fibrates. The treatment in hyperlipidemia given to the patient is for a long period; hence during that time patients remains dependent on the oral dosage form. About 60% of the drugs used in the management of hyperlipidemia are poorly water-soluble, especially BCS (Biopharmaceutical Classification System) class II drugs. The BCS II drugs are poorly soluble but highly permeable owing to which these drugs have solubility dependent absorption [5]. However, most of the drugs absorb up to the ileum part of the gastrointestinal tract. This narrow absorption window for the oral route makes it a challenging task to design and develop a pharmaceutical formulation of a poorly water-soluble drug [6, 7]. Hence this is a challenge for the pharmaceutical professionals to enhance the solubility of the antihyperlipidemic drugs. The reported literature shows that researchers have tried several techniques to enhance the solubility of poorly water-soluble drugs based on physical or chemical modifications of a drug. Some of these methods are like particle size reduction, crystal engineering, salt formation, complexation and so forth [8-12]. During the last decade, numerous published research papers showed increased interest of researchers in solid dispersion technology. During this time, many marketed products approved by the United States Food and Drug Authority (USFDA) showed the potential of solid dispersion technique. Most of the drugs used in the treatment of hyperlipidemia are poorly water-soluble drugs like gemfibrozil, atorvastatin, simvastatin, fenofibrate, etc.

Solid dispersions started from the 1960s when Sekiguchi and Obi reported first solid dispersion called eutectic mixture [13]. After that Levy and Kanig reported solid solutions with the reduced particle size of the active pharmaceutical ingredient with excipients [14, 15]. In 1965, Goldberg *et al.* differentiated between the eutectic mixtures and solid solutions listing the advantages of solid solutions over eutectic mixtures [16]. Bates prepared solid dispersions of reserpine-PVP by solvent evaporation method and described it "co-precipitates" [17]. Simonelli and co-workers defined the term "co-precipitation" process more precisely by preparing a solid dispersion of sulphathiazole and PVP [18]. Later on, Chiou and Riegelman defined it as a solid dispersion of active ingredient within the matrix system form by one or more inactive ingredients [19]. In solid dispersions drug may disperse up to the molecular level in a matrix system made from one or more carriers; finally, the formulation attains amorphous, partially amorphous or crystalline form. The key advantage of the solid dispersions is that these enhance the solubility of drugs having low water solubility especially BCS Class II drugs, by changing the physical properties (surface area, wet ability, crystal habit, etc.). Excipients present in the formulation reduce agglomeration of the active ingredient by dispersing it and prevent the formation of any water-insoluble surface layers around particles [20]. Solid dispersion technique also offers several advantages over other techniques because of its simplicity in process, formulation, no use of toxic excipients and may reduce the pre-systemic metabolism of the drug. It is also easy to fill these in the capsules or to make a tablet of solid dispersions which makes it easy and economical to scale up the manufacturing process. Some of the methods used in the preparation of solid dispersions are described below.

Melting method

In the melting method, the drug and hydrophilic polymers are mixed and heated to temperatures above the eutectic point in an open or closed environment by any conventional means or using microwaves [21-24]. After the complete miscibility of drug and polymer, this mixture is cooled quickly to get the maximum amount of amorphous solid form [25-27]. The finally obtained solid mass is crushed, pulverized and sieved to get the powder form of solid dispersion [26, 28]. This method is suitable for drugs that do not change physiochemical properties at a higher temperature. In 2013, patent no. WO 2013036053A2 was granted to Samyang Biopharmaceuticals Corporation, Seoul (Korea), for Solid dispersions of tacrolimus prepared with Polyethyleneglycol-6000 and Poloxamer-188 in the ratio (1:1:1 to 1:1:3) by melt method. The optimized solid dispersion formulation exhibited enhanced bioavailability as compared to marketed product Prograf D [29]. The patent US 9,101,617 B2 describes the method of preparing solid

dispersions of nifedipine with polyvinyl alcohol "POVACOAT type-F" prepared by microwave melting method. In solid dispersions of nifedipine, the API was present in amorphous form as compared to the crystalline form observed in pure API [30].

Hot-melt extrusion

The hot-melt extrusion method is an extended application of the melting method. The main advantage of this method is that it is solvent-free, in which, the drug and carrier are simultaneously mixed, heated, melted, homogenized, cooled and extruded in the form of rods, pellets and tablets for different purposes [25, 31]. Shear forces in the machine disaggregate the drug particles in the molten polymer by rotating screw(s), resulting in the formation of homogenous dispersion obtained from the cooling track [25, 32]. This process involves the transformation of a solid mass of intertwined particles into a viscous liquid or semisolid mass by heating and intense mixing [33]. Sometimes there may be a problem regarding the miscibility of drug and polymers, in such condition use of miscibility enhancers like Kollidon VA64, Soluplus and Eudragit EPO may solve this problem [34]. A modified version of hot-melt extrusion is "Nano-Extrusion" process in which suspension of the drug is prepared first and then processed with a polymer with the help of hot-melt extrusion. Solid dispersions obtained by this method are supersaturated amorphous solid dispersions [35]. The Chinese patent (CN103202811A) is related to the enhancement of solubility of poorly water-soluble drug diflunisal by preparing solid dispersion [36].

Melt agglomeration

Melt agglomeration method is a superior approach compared to conventional melt method which poses problems like poor flow and compressibility properties due to softness; stickiness of the solid dispersions act as a barrier for their applications on a large scale of oral dosage formulation [37]. In Melt agglomeration method mixture is prepared with high shear mixers or the rotary processor by three ways: adding the molten carrier containing the drug to the heated excipients, adding the molten carrier to a heated mixture of the drug and excipients or heating a mixture of the drug and carrier to a temperature within or above the melting range of the carrier [38, 39]. Rotary processor with high shear is more preferable due to its automatic control on temperature, which incorporates more binder content in agglomerates [39]. Seo *et al.,* (2003) prepared the agglomerates containing solid dispersions of diazepam by melt agglomeration in a high shear mixer. The study reported significant higher dissolution rate obtained with a lower drug concentration indicating a higher degree of molecular dispersion at the lower concentration [38]. The patent WO2004073687 demonstrates the solid dispersion fabrication through melt agglomeration method by use of a poor water-soluble pharmaceutical active ingredient with macrogol 1500 and silicon dioxide [40].

Solvent evaporation method (solvent method)

In this method, drug and carrier are dissolved in a common solvent or separately in two different organic solvents and finally mixed to achieve maximum interaction up to the molecular level. After complete dissolution, the solvent is evaporated naturally or with the help of a suitable instrument like spray dryer, Electrospinning, rota-evaporator, etc. After drying solid mass obtained is ground, sieved and dried. The selection of the solvents depends upon the physical properties of the drug and excipients. The solvents most commonly used are methanol, ethanol, ethyl acetate, methylene chloride, acetone, water and mixtures thereof. The main advantage is that this method is superior to other methods (fusion or melts method) because of more miscibility at the molecular level and higher rate of evaporation than the rate of nucleation [41]. A Canadian patent number CA2778981C disclosed the method of preparation of solid dispersion of an antibiotic rifaximin used in the traveller diarrhea [42]. According to this concept, various methods are available to prepare solid dispersions such as Co-Precipitation Method, Spray Drying Method, Fluid Bed Coating Method, Vacuum Drying and Rotary Evaporation, Cryogenic Techniques, Freeze-drying, Electrospinning Method, Supercritical Fluid Technology, etc.

Co-precipitation method (co-evaporates)

This process is preferable over the melting method because it gives more porous solid dispersions with the larger surface area along with a faster dissolution rate [43]. Most of the methods require a common solvent for solvent evaporation in which drug and carrier are miscible, but this method does not have such a requirement. This advantage broadens the application to a large number of drugs as well as excipients. In this method accurately weighed hydrophilic carrier is dissolved in water and the drug is dissolved in an organic solvent. After complete dissolution, the aqueous solution of the carrier and the organic solution containing the drug are mixed to form a transparent solution. This transparency shows the maximum interaction between the drug and exipient(s). After that, this mixture is heated and evaporated. Finally, this dispersion is pulverised with pestle and mortar, sieved and dried. An Australian patent AU2015295073B2 was granted to Hovione International limited (Portugal). This patent disclosed the preparation of submicron size solid dispersion using co-precipitation method [44].

Spray drying method

Spray drying is a fast method for the preparation of solid dispersion. An accurately weighed amount of drug with the hydrophilic carrier is dissolved in an organic solvent like ethanol, methanol, dichloromethane or a mixture of solvents to obtain a solution or suspension. After that a pump system is used to transfer this solution or suspension from the container to the nozzle containing atomiser. This atomisation depends upon the design of atomiser such as rotary atomisation, pressure atomisation, pneumatic atomization [45-47]. Simultaneously, these droplets of solution come in contact with hot air passing through the same path and transform it into powdered solid dispersion. The United States patent US 9,339,467 B2 is related to the development of the solid dispersion through modified spray drying technique for preparation of amorphous solid dispersion [48].

Freeze drying

This method is suitable for the drugs, which are sensitive to temperature and deteriorate at a higher temperature. This method includes freezing, followed by lyophilization. In this method, drug and carrier are dissolved in a common solvent. After that this mixture is allowed to freeze, and the fully frozen solution or suspension is then lyophilized. The solid dispersion finely obtained may be present in the form of amorphous or partially amorphous powder [49]. In this method, the freezing rate is significant to control phase separation. The main advantage of freeze-drying is that it immobilizes the drug molecules and prevents it from setting up in the crystalline domain hence stops the formation of the crystalline phase. The selection of the solvent(s) should be done carefully because most of the organic solvents have low freezing point and stability problem during the sublimation process. In 2014, a patent (US 8,722,091 B2) on solid dispersion was granted to Baxter International Inc., Deerfield, IL (US) for preparation of submicron-sized nano-particles of itraconazole by lyophilisation technique [50].

Vacuum drying and rotary evaporation

In a vacuum and rotary drying, drying is achieved at a moderate temperature and under vacuum to avoid the risk of degradation of drugs and carriers at high temperature. The rotary apparatus attached with a vacuum pump is used for this purpose. After solvent evaporation process, the resultant solid dispersions may be stored in a desiccator for complete removal of residual solvent. This process takes a long time due to which chances of phase separation and re-crystallisation of the drug may dominate. In 2014, Patent no. CN103191439B was granted to Shenyang Pharmaceutical University China. The solid dispersion of silybin with ursodeoxycholic acid (molar ratio of 1:0.5 to 1:5) was prepared by solvent method or milling prepared. This solid dispersion of drug is present in an amorphous state, compared with the original drug, silybin. The dissolution rate of the solid dispersion significantly increased with a significant improvement in oral absorption [51].

Fluid bed coating method

In this method, the drug and carrier are mixed in an organic solvent; this mixing is done manually but sometimes may be assisted with sonication. After that, this mixture is coated on the non-pareil cores

made of sugar or inert PVC pallets by using a fluid bed coater. Inlet temperature, airflow rate, spray rate, atomising air pressure and spray nozzle diameter are some critical parameters of the process which affect the coating. Zhang *et al.,* (2008) prepared a solid dispersion of lansoprazole and PVP by fluid-bed coating technique which exhibited approximately 80% drug release in 5 min [52]. The advantage of this technique is that pallets are compressible in the form of tablets, hence easy for technology transfer for commercial scale. A United States patent, no. US 2007/0248681 A1 discloses fluid bed coating method for preparing solid dispersions of a poorly water-soluble drug (undisclosed) [53].

Cryogenic techniques

Cryogenic techniques are fast as compared to other technologies, used in producing nanostructured amorphous drug particles. The rapid rate of freezing prevents molecules from settling in the crystalline domain and provides a high porosity in the formulation. In cryogenic processing, dry powder solid dispersions are prepared through two different processes such as spray freezing into cryogenic Liquids (SFL) and spray freezing onto cryogenic fluids. These two processes are known as spray freezing and ultra-rapid freeze-drying [54, 55]. After the freeze-drying or ultra-rapid freezing, this suspension is transferred to a non-insulated beaker for evaporation of cryogenic fluid. After evaporation residual is freeze-dried or vacuum dried to get a fine dispersion [54]. A Chinese patent CN107375219A describes the preparation of solid dispersions of a Chinese traditional medicine "tanshinone IIA-hydroxyapatite (HAP)" to enhance its solubility by spray freezing method [56].

Electrospining method

The electrospining technology used in the polymer industry is a combination of solid solution and dispersion technology with nanotechnology. In normal single needle electrospining, a liquid stream of a drug/polymer solution is subjected to a potential between 5 to 30 kV. In contrast, in high-speed Electrospinning, 50kV is applied, comprising a stainless steel spinneret [57]. When electrical forces prevail over the surface tension of the drug/polymer solution at the air interface, evaporation of solvent from drug and carrier takes place. During this time, molecules of the drug with carriers align toward the electric field and produce the fibres of submicron or nano diameters. Fibres can be collected on a screen in the form of a nonwoven fabric, or from a spinning mandrel [58]. This technique has powerful potential for preparing nanofibres with amorphous nature and controlling the release of medicine, as it is simplest and the cheapest. This technique can be utilized for fabricating solid dispersions in future [59]. A patent, CN102218019B demonstrated the preparation of nanoparticulate solid dispersion of paracetamol by electrostatic spraying [60]. Another patent CN101664380A demonstrates the preparation of solid dispersions of Acyclovir, ketoconazole and tofu (Chinese traditional medicine) by electrospining method [61].

Supercritical fluid technology (SCF)

The phase separation is a challenging task during the preparation of solid dispersion. The supercritical fluid technology has emerged as a lucrative approach to tackle this problem. These fluids exist as a single fluid phase above their critical temperature and pressure. The CO_2 is most preferably used because of its non-toxic, non-flammable and chemically inert nature. Riekes *et al.* (2015) prepared a solid dispersion of nimodipine with PVP K 30 by supercritical fluid technology. The dissolution study of optimized formulation showed that about 100% of drug was released within 5 min with a remarkable decrease in mean arterial pressure during the *in vivo* study [62]. A Patent CN104069066A describes the preparation method for the solid dispersion of Berberine-sodium caprate by supercritical fluid technology [63].

Co-precipitation with supercritical fluid

There are various conventional methods for preparing solid dispersion, based on the fusion or solvent processes, but supercritical fluid processing (SCP) has emerged as an alternate solvent evaporation method. This method is used for preparing co-precipitates of smaller particle size, lower residual organic solvent and better flow ability. A supercritical fluid is that fluid which exists as a single fluid phase above its critical temperature and pressure. Carbon dioxide is most frequently used as supercritical fluid because of its low critical temperature which makes it attractive for processing heat-sensitive pharmaceuticals. During this processing rate of cooling and solvent removal is controlled, resulting in acceptable batch-to-batch variation important for manufacturing point of view [64]. In this method, the drug is mixed with the organic solvent stored in the preheated chamber attached with an air pump. This mixed solution is passed through an inner capillary. Simultaneously, liquid carbon dioxide gas is passed through a collar nozzle situated outside of inner capillary to the precipitation chamber. The drug solvent and CO_2 gas come in contact with each other at high pressure in the precipitation chamber and this high pressure reduces the solvation power of the solution, and a supersaturation develops for a short time segment. After that, this supersaturation produces precipitation which can be seen in the form of cloudiness from the transparent window. After the completion of the precipitation, the precipitation chamber is depressurized as per experimental conditions. Finally, solid dispersion is collected from the collector and store in a desiccators [65]. A patent AU 2015295073 B2 describes the fabrication of nano-amorphous solid dispersion of carbamazepine with Eudragit L 100. This solid dispersion was prepared by co-precipitation method using supercritical fluid technology. The *in vitro* and *in vivo* study suggested that solubility and bioavailability were enhanced as compared to that of the micro-amorphous and crystalline form of API [44].

Melt-solvent method

In the melt-solvent method, an accurately weighed amount of drug is dissolved in an organic solvent. Finally, this solution is mixed into the melt of the carrier by pouring into it. It is then quickly cooled. The mass is kept in a desiccator for complete drying. The solidified mass is crushed, pulverized and passed through a sieve [65]. A Chinese patent CN1559606A described the solid dispersion prepared by the melt-solvent method for cyclosporine-A [66].

Co-grinding method

The strain produced by the high level of mechanical energy is a fundamental basis for the preparation of balled milled solid dispersions. This strain may perform the phase transition process and convert the crystalline state to the amorphous state of powder [67]. In this method, drug and the carrier are physically mixed using a blender at an adequate speed, and then this mixture is transferred in a vibration ball mill chamber. After that, the combination is ground for a specific time by adding steel balls in it [68].

Dropping solution method

The dropping method facilitates the crystallization of different chemicals and produces round particles from melted solid dispersions. For a laboratory-scale preparation, a melted drug-carrier mixture is dropped on a cooling plate with the help of pipette, where it solidifies into round particles. The size and shape of the particles depend upon viscosity of the melt and the size of the pipette. It is very important to adjust the temperature so that when the melt is dropped onto the plate, it solidifies to a spherical shape because viscosity is highly temperature-dependent [69]. The literature review shows that until now, no patent has been granted under this procedure by any patent authority.

Gel entrapment technique

Carrier is dissolved in an organic solvent to form a clear and transparent gel. Then the drug is dissolved in a gel by sonication for a few minutes. After that organic solvent is evaporated under vacuum; resulting solid dispersion is obtained reduced in size by glass mortar and sieved [70]. Literature studies show that only research reports exist, but so far no patent has been granted under this process under this procedure.

Recent advancements in solid dispersions of anti-hyperlipidemic drugs

During the recent three decades, numerous research articles based on solid dispersion techniques of antihyperlipidemic drugs have

been published. The main objective of most of the studies was to design and develop solid dispersions to enhance solubility and stability. In these attempts, several solid dispersions of antihyperlipidemic drug candidates have been developed by researchers using various methods like solvent evaporation, melting method, freeze-drying method, etc. Some recent advancements in this field of antihyperlipidemic drugs are discussed here. Ambike *et al.,* (2005) reported solid dispersions of simvastatin prepared by the spray-drying method. Simvastatin with aerosil 200 and PVP k 30 (1: 1; 1: 1: 1 and 1: 2: 2 ratio) were dissolved in dichloromethane and then spray-dried by a spray dryer. The solid dispersion with ratio 1: 2: 2 was found to enhance dissolution because of hydrogen bonding between simvastatin and silanol group of Aerosil 200. A 14 d *in vivo* study showed that after seven days cholesterol level decreases by three times and after14 d twice as compared with the reference drug [71]. In another similar investigation by Thybo *et al.,* (2008) solid dispersions of antihyperlipidemic drug probucol with PVP K30 were found having enhancement of dissolution as well as stable up to 12 mo at 25 ºC and 60% Relative Humidity [72].

Srinarong *et al.* (2009) reported stable solid dispersion tablets of fenofibrate with inulin 4kDa by lyophilization method formulation. The tablets were found stable for three months at 40 ºC and 75% Relative Humidity [73]. He *et al.,* (2010) investigated solid dispersions of fenofibrate with Eudragit E100 by hot-melt extrusion method. The *in vitro* and *in vivo* demonstration showed increased in solubility as well as were more bioavailable as compared to marketed product [74]. The bioavailability enhancement is the second objective after the solubility parameter for a BCS II drug. With this aim Yang *et al.,* (2015) used krill oil as a source of the omega-3 phospholipids to enhance the bioavailability of fenofibrate because omega-3 phospholipids facilitate the permeability of the intestine. Yang and co-workers prepared the solid dispersions of fenofibrate with krill oil by antisolvent precipitation method. The dispersion showed complete dissolution within 15 min and 6-7 fold increment in bioavailability [75].

Patel *et al.* (2019) prepared a solid dispersion of Lovastatin with Modified Locust Bean Gum through a solvent evaporation method in ratio from 1:1 to 1:5. The 1:5 ratios showed more dissolution as well as a significant HMG coenzyme reductase activity [76]. Similarly, Li *et al.* (2019) prepared solid dispersions with kaempferol (a flavonoid) showing enhanced bioavailability [77].

Kim *et al.* (2013) designed a supersaturated solid dispersion of PVP VA64 and atorvastatin. These dispersions of atorvastatin showed increased dissolution and absorption [78]. Another study reported that interactions between atorvastatin and PVP K30 might cause dissolution enhancement. In this study, there was a significant decrease in the liver's steatosis, with an increase in oral absorption [79, 80]. All these, along with some other studies with primary points of the literature are summarized in table 1.

Table 1: A brief overview of literature of antihyperlipidemic drugs solid dispersions showing *in vitro* and *in vivo* activity

Drug	Type of study	Particulars	Method	Ref.
Gemfibrozil	*In vitro* study	Solid dispersions with Syloid 72 were found to enhance solubility, and with syloid AL-1 found more stable during stability study.	Microwave method	[81]
Gemfibrozil	Cell line study	The study report suggested the use of sucrose laurate (D1216) 5-10% in an oral dosage form.	Melting method	[82]
Probucol	*In vitro* study	Solid dispersions prepared with PVP K30, were found to enhance dissolution and stability for one year at 25 ºC, 60% relative humidity.	Spray drying	[72]
Probucol	*In vitro* study	Solubility enhanced in ternary solid dispersion was found due to molecular bonding between probucol and Eudragit E PO and Eudragit E PO with saccharine.	Co-grinding	[83]
Probucol	*in vivo study*	The study showed more bioavailability of solid dispersion as compared to pure drug.	Solvent melting method	[84]
Probucol	*In vitro*	The formulated solid dispersion was stable in the heat shield container for 5 mo.	Solvent evaporation	[85]
Lovastatin	*In vitro* and *in vivo study*	Enhancement in dissolution depended upon the preparation method and HMG Co-A reductase activity was significantly lowered.	Solvent evaporation	[76]
Lovastatin	*In vitro study*	Solid dispersion with Pluronic F127 resulted in 30-fold solubility improvement and drug release 85–100% within 30 min.	Kneading method	[86]
Lovastatin	*In vitro* and *in vivo study*	Solid dispersion with kaempferol and lovastatin enhanced the bioavailability of lovastatin up to 3.79 fold.	Solvent evaporation	[77]
Lovastatin	*In vitro* study	Solubility enhancement was reported in formulation prepared with acetylsalicylic acid.	Co-grinding method	[87]
Fenofibrate	*In vitro*	Eutectic formulation with Pluronic-127 enhanced solubility up to 134 fold.	Fusion method	[88]
Fenofibrate	*In vitro* and *in vivo study*	Solid dispersion formulation with Eudragit E100 was found to improve solubility as well as more bioavailability in comparison to a marketed product.	Hot-melt extrusion	[74]
Fenofibrate	*In vitro study*	Researchers reported the wetting effect of the carrier on the dissolution of the drug.	Solvent evaporation	[89]
Fenofibrate	*In vitro* and *in vivo study*	The published report showed complete dissolution in 15 min and was found to 6-7 folds more bioavailable than pure drug.	Aantisolvent precipitation technique	[90]
Fenofibrate	*In vitro* and *in vivo study*	Researchers reported the solid dispersion with PVP and SLS released 75% of the drug within 30 min.	Spray-drying technique	[91]
Fenofibrate	*In vitro* and *in vivo study*	The study found formulation with greater surface area and increased bioavailability during *in vivo* studies.	Thin film freezing method	[92]
Fenofibrate	*In vitro* study	The study reflected that solid dispersion tablets with inulin 4 kDa gave faster dissolution and well as good stability.	Lyophilization	[73]
Atorvastatin	*In vitro* and *in vivo study*	The researcher's study demonstrated that Neem Gum was effective in solubility as well as bioavailability enhancement of atorvastatin.	Solvent evaporation	[93]
Atorvastatin	*In vitro* study	Research report showed significant improvement in dissolution rate.	Solvent evaporation	[94]
Atorvastatin	*In vitro study*	In published report solid dispersion released 80% of the drug within 15 min.	Co-grinding method	[95]
Simvastatin	*In vitro study*	The study report suggested that significant improvement of dissolution was due to change of drug from crystalline state to amorphous state.	Co-evaporation	[96]
Simvastatin	*In vitro* and *in vivo study*	Research report showed drug changes in amorphous form with significant improvement of therapeutic efficacy of the drug.	Spray drying	[71]
Simvastatin	*In vitro* and *in vivo study*	Researchers found the enhancement of *in vitro* solubility as well as *in vivo* antihyperlipidemic activity of the drug.	Solvent evaporation	[97]
Atorvastatin	*In vitro* and *in vivo study*	Report showed 33% increase in solubility and about 3 fold increase in the potential to lower lipid level.	lyophilization	[98]

Drug	Type of study	Particulars	Method	Ref.
Atorvastatin	*In vitro* and *in vivo study*	Solid dispersion with PVP VA 64 showed enhanced supersaturation as well as oral absorption.	Supercritical sntisolvent (SAS) process	[78]
Atorvastatin	*In vitro* and *in vivo study*	Dispersion with PVPk30 showed a remarkable effect in liver steatosis and therapeutic potential with the enhancement of dissolution.	Solvent evaporation	[79]
Atorvastatin	*In vitro study*	Solid dispersion with PVP k30 showed the interaction of drug and polymer with the change of drug crystalline to amorphous form.	Electrospraying method	[80]
Atorvastatin	*In vitro* and *in vivo study*	The research report showed more than 90 % of drug release within 15 min and formulation was 83% more bioavailable as compared to marketed product "Lipitor".	co-precipitation method	[99]
Simvastatin	*In vitro*	Enhancement of dissolution was due to change in the morphological character of the drug in amorphous form.	Spray drying and Hot melt Extrusion	[100]

Recent patents on antihyperlipidemic drug solid dispersions

In recent decades several patents on solid dispersion techniques have been granted. However, only a limited number of patents have been granted for BCS class II antihyperlipidemic drugs. These patents also support the potential of this technique to increase stability and bioavailability to some extent, along with poor water solubility.

The patent CN105164162B dealt with the antihyperlipidemic drugs probucol and phyntoin-noticum with esterified cellulose by spray drying method; this patent described that esterification produces saturated solid dispersions with increased solubility [101]. Similarly, in another patent CN105308081B, the inventor prepared an amorphous solid dispersion of the probocol by the spray-drying method [102].

A Chinese patent CN104306343A described the importance of a resin in a solid dispersion of atorvastatin, which binds alkaline agents within it. This resin prevents the release of alkalizing agents to the stomach and was found to be very effective in abdominal discomfort [103]. Besides, another Chinese patent CN104546775A gave information about the method of preparing a solid dispersion of atorvastatin using polydone and aerosil. These solid dispersions did not contain any alkaline substance which causes stomach upset and were found to be stable for six months [104. Apart from these, another Chinese patent CN104306343B disclosed the method of making atorvastatin solid dispersion micro pills that can be compressed into tablets [105].

A Chinese patent CN103690504A described preparing rosuvastatin calcium tablets of solid dispersion. Inventor first prepared solid dispersion of rosuvastatin by using MCC and lactose by spray drying. After that, these solid dispersions were mixed with some excipients to prepare granules which were further compressed to make tablets. The formulation was more stable than reference at a temperature of 60 °C, humidity 92.5%, 4500±500LX illumination condition ten days study [106]. Similarly, in another Chinese patent, CN105147636A inventor prepared solid dispersion formulations of rosuvastatin by the use of microcrystalline cellulose which were stable for six months [107].

US patent US8329214B2 provided information about preparing fenofibrate solid dispersion with PVP and SLS [108]. In this series, another patent US6465011B2 disclosed information regarding the preparation of solid dispersion of fenofibrate with IRB-88 by the spray-drying method [109]. Some important facts of the patents of antihyperlipidemic drugs solid dispersions are reported in table 2.

Table 2: An overview of reported patents related to antihyperlipidemic drugs solid dispersions

S. No.	Name of the drug	Patent number	Application year	Description	Reference
1.	Probucol	CN105164162B	2017	The esterification with omega-3phospholipids produced saturated solid dispersion with enhanced solubility.	[101]
2.	Probucol	CN105308081B	2017	Inventor prepared amorphous solid dispersion of probucol.	[102]
3.	Simvastatin/ camsylate	JP2009521526B	2020	Complex formulation comprising amlodipine camsylate and simvastatin and method for preparation thereof.	[110]
4.	Atorvastatin	CN104306343A	2017	One kind of atorvastatin calcium tablets that reduced the problem of alkaline material as well as reduced discomfort of the stomach by locking alkaline material in the resin present in the tablet	[103]
5.	Rosuvastatin	CN105147636A	2018	Inventor prepared solid dispersion capsules of Rosuvastatin calcium with microcrystalline and preparation were found more stable after accelerated 6 mo study.	[107]
6.	Rosuvastatin	CN103690504A	2018	Inventor prepared rosuvastatin calcium solid dispersion tablet which was stable at temperature of 60 °C, humidity 92.5%, 4500±500LX illumination condition for 10 d.	[106]
7.	Finofibrate	US8329214B2	2018	Fenofibrate tablets were compressed from solid dispersion prepared with a fluid bed dryer that showed high dissolution along with high bioavailability.	[108]
8.	Atorvastatin calcium	CN104306343B	2017	Inventor prepared Micropill solid dispersion tablets.	[105]
9.	Atorvastatin calcium	CN104546775A	2017	Solid dispersion formulation without any basic or alkaline material. Fast release even after 6 mo of accelerated stability study.	[104]
10.	Finofibrate	US6465011B2	2002	Solid dispersion with enhanced in dissolution as well as bioavailability.	[109]
11.	Atorvastatin/ Torcetrapibo	US8828438B2	2014	Amorphous solid dispersion with HPMCAS-MG and found 60% of drug was in amorphous form.	[111]

Usfda approved marketed solid dispersion products

During recent years among the solubility enhancements techniques, solid dispersion technique is widely used because of its easy scale-up and economic nature. Various researchers have established some formulations in an amorphous form with enhanced solubility as well as stability. In some studies it was reported that solid dispersions might enhance the bioavailability of poorly soluble drugs. Several formulations, whether capsule or tablet, have been developed and marketed with the help of this approach. World-leading Food and

Drug Authority "USFDA" approved several formulations on solid dispersions based technique. These include Tpoxx (Tecovirimat), Imbruvica (ibrutinib), Ingrezza (valbenazine), Rydapt (midostaurin), etc. In the past three years, from 2016 to 2018, USFDA approved formulations in the form of tablets or capsules for different therapeutic classes, mentioned in table number 3 here.

Table 3: List of marketed formulation approved by USFDA during 2016-2018

Patent no.	Company name	Markted name	Formulation	Ref.
AU2014290333B2	Siga Technologies Inc.	Tpoxx (Tecovirimat)	Capsule (2018)	[112]
US20180028537A1	Patheon Development Services Inc (f/k/a Agere Pharmaceuticals Inc), Pharmacyclics LLC	Imbruvica (ibrutinib)	Capsule (2017)	[113]
US20170360874A1	Gilead Pharmasset LLC	Vosevi (sofosbuvir, Velpatavir)	Tablet (2017)	[114]
WO2018093717A1	AbbVie	Mavyret (glecaprevir/pibrentasvir)	Tablet (2017)	[115]
EP2054040B1	Novartis	Rydapt (midostaurin)	Capsule (2017)	[116]
WO2018218233A1	Exelixis, Inc.	Cabometyx (cabozantinib)	Tablet (2016)	[117]

Future developments of antihyperlipidemic solid dispersions

In recent years, many researchers have utilised solid dispersion approach as most preferable among pharmaceutical researchers to enhance the solubility, stability and enhancement of bioavailability. Researchers have fabricated several solid dispersions of poor water-soluble antihyperlipidemic drugs through several methods like hot-melt extrusion, microwave method, spray drying, electrospinning methods, etc. as these techniques are good and productive. However, solid dispersions have some stability issues like crystal growth. This problem can be minimised with the suitable selection of drug and polymer ratio. The major advantage of the solid dispersion is that it is easy to fabricate in oral dosage forms like capsules, tablets and pellets. A variety of the pharmaceutical solid dispersion formulation approved by the USFDA in recent years show the success of the solid dispersion technique as compared to the other solubility enhancement technique like co-crystallisation, salt formation, nanosuspension, etc.

CONCLUSION

Research reports published by researchers suggest that it is a challenging task to develop a pharmaceutical formulation for a poorly soluble active drug component belonging to an antihyperlipidemic class. This review is a compilation of the many approaches used for the solid dispersions of the antihyperlipidemic drugs. Various researchers have prepared solid dispersions of antihyperlipidemic drugs with different polymers to enhance solubility, bioavailability and stability by classical or novel methods. Atorvastatin solid dispersion shows a remarkable pharmacological effect in steatosis of the liver. Long-term therapy in hyperlipidemia may cause side effects because of the use of an alkaline substance present in the marketed atorvastatin tablet that produces discomfort of the stomach. A patent CN104306343A describes the importance of a resin in a solid dispersion of atorvastatin, which binds alkaline agents within it. This resin controls the release of alkalising agents to the stomach and makes it very useful in abdominal discomfort[103]. In this series, patents with patent no. CN105147636A, CN103690504A solve the problem of stability related issues of the rosuvastatin by preparing solid dispersions. The main advantage in the preparation of solid dispersions of the antihyperlipidemic drug is their low dose. This low dose of the active pharmaceutical product allows the use of a higher amount or more number of excipients to obtain the effective drug-excipients ratio for a formulation. This technique gives the advantage of using numerous already established excipients and ease in scale-up manufacturing. So there is no need for toxicity testing of these products and knowledge of established excipients also helps in scale-up manufacturing techniques of solid dispersion products. The emergence of advanced manufacturing techniques in this era also helps to achieve enhancement of quality of solid dispersions as compared to the classical methods. The above discussion pertains to all techniques used for the preparation of solid dispersions and patents reflect that solid dispersion techniques have proved as an effective approach to solve the solubility, bioavailability and stability related issues of antihyperlipidemic drugs.

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CONFLICT OF INTERESTS

Declared none

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