Solid Dispersion: A Recent Update

Midha K1*, Rani P1, Arora G1, Nagpal M1, Kalra S2

1Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India
2Skies Institute, Rajpura, Punjab, India

*Corresponding author: Midha K, Chitkara College of Pharmacy, Chitkara University, Rajpura, Punjab, India, E-mail: kanavmidha@gmail.com

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Abstract

Solid dispersions have engrossed substantial attention as an effectual means of refining the dissolution rate and hence the bioavailability of a variety of hydrophobic drugs. In this review, it is intended to discuss the future prospects related to the area of solid dispersion manufacturing. Improving oral bioavailability of drugs those given as solid dosage forms remains a challenge for the formulation scientists due to solubility problems. The dissolution rate could be the rate-limiting process in the absorption of a drug from a solid dosage form of relatively insoluble drugs. Therefore, increase in dissolution of poorly soluble drugs by solid dispersion technique presents a challenge to the formulation scientists. Solid dispersion techniques have attracted considerable interest of improving the dissolution rate of highly lipophilic drugs thereby improving their bioavailability by reducing drug particle size, improving wettability and forming amorphous particles. This review article discusses the various preparation techniques and characterization for solid dispersion and compiles some of the recent technology transfers in the form of patents.

Keywords: Solid dispersion, Carrier, Solubility, Bioavailability, Dissolution enhancement.

Introduction

Oral bioavailability of drugs depends on its solubility and/or dissolution rate, therefore major problems related to these drugs was its very low solubility in biological fluids, which consequences into poor bioavailability after oral administration [1-5]. A drug with deprived aqueous solubility will typically demonstrate dissolution rate limited absorption, and a drug with poor membrane permeability will typically reveal permeation rate limited absorption [6].

problems of these drugs and methods for triumph over the solubility limitations are recognized and applied commercially so that potential remedial benefits of these dynamic molecules can be realized [10]. Consequently, many efforts have been made to improve dissolution of the drug. Methods accessible to enhance dissolution take in salt formation, micronization and addition of solvent or surface active agents. Solid dispersion (SD) is one of such methods and encloses a dispersion of one or more active component in an inert carrier or matrix in the solid state organized by melting, dissolution in a solvent or melting-solvent method [2,11]. The formulation of drugs having low aqueous solubility using solid dispersion equipment has been an active area of research since 1960 [12]. Among the various approaches to enhance solubility, the solid dispersion (SD) technique has often proved to be the most victorious in improving the dissolution and bioavailability of poorly soluble drugs as it is simple, economic, and advantageous [13]. Solid dispersion means an assembly of solid products consisting of at least two different ingredients, generally a hydrophilic inert carrier or matrix and a hydrophobic drug. The carrier can be either crystalline or amorphous in nature. Most frequently used carriers for the preparation of SDs are a diverse grade of polyethylene glycols (PEGs) and polyvinylpyrrolidone (PVPs), Gelucire 44/14, Labrasol, sugars, and urea [14-16]. The drug can be isolated molecularly, in amorphous constituent part (clusters) or in crystalline constitute part [2]. The first drug whose rate and degree of absorption were considerably enhanced using the solid dispersion technique were sulfathiazole by Sekiguchi and Obi [1]. The advantages of solid dispersion over conventional tablets of capsules can be summed up in Figure 1. This method has been used by many researchers/scientists for a wide variety of poorly aqueous soluble drugs to improve the solubility of the drugs and hence bioavailability [13]. Literature reviews on the solid dispersion of past four decades propose that there is an increasing interest in using this advance [5]. Despite an active research interest, the number of marketed products arising from this approach is unsatisfactory. Only a few profitable products were marketed during the last four decades [1,17,19].

**Classification of Solid Dispersion**

The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles by melting or solvent method. Therefore, based on their molecular arrangement, different types of solid dispersions (SDs) can be distinguished. They are described in Table 1 [20].

**Mechanism of Drug Release from Solid Dispersion**

There are two main methods of drug release from immediate release solid dispersions, which include drug-controlled release and carrier controlled release. When solid dispersions are isolated in water, the carriers often soften or absorb water quickly due to their hydrophilic property and form concentrated carrier layer or gel layer in some cases. If the drug liquefies in this layer and the viscosity of this layer is high sufficient to prevent the diffusion of the drug during it, the rate-limiting step will be the diffusion of the carrier into the bulk phase and this method is carrier-controlled release. If the drug is unsolvable or sparingly soluble in the concentrated layer, it can be released intact to contact with water and the dissolution outline will rely on the belongings of drug particles (polymorphic state, particle size, drug solubility) [21]. In fact, these two methods often occur simultaneously because the drug may be partly soluble or deceived in the concentrated carrier layer. On the other hand, these methods said to explain the different release behaviours of solid dispersions and figure out the way to enhance the dissolution profile of solid dispersions. Copious researches showed the perfection of drug dissolution profile when the ratio of carriers in solid dispersions was increased because the drug was dispersed better and the drug crystallinity diminished [22]. In these solid dispersions, the main release mechanism is drug-controlled release. In compare, other researchers established the decrease in drug dissolution rate when the ratio of the carrier in solid dispersions was improved [23]. This can be clarifying by the carrier-controlled mechanism in which the

A gel or concentrated carrier layer is formed and performs as a diffusion barrier to delay drug release. The release mechanism may also be exaggerated by the ratio of drug–carrier in solid dispersions. Karavas et al. [24] prepared felodipine solid dispersions by using diverse types of PVP, PEG as carriers and accomplished that the percentage of the drug in solid dispersions resolve the mechanism of drug release which was drug diffusion (through the polymer layer)-controlled at low drug contents and drug dissolution-controlled at high drug contents. Consequently, in order to enhance the dissolution profile of solid dispersions, it is significant to identify the mechanism release of solid dispersions rather than only focus on the polymorphic state of drugs as in carrier-controlled release solid dispersions, the carrier properties such as solubility, viscosity, gel forming ability and the ratio of drug–carrier are the key factors affecting the drug dissolution profile. In CRSD, rely on the characteristic of polymers and the miscibility of the drug and carrier there are two main methods by which the drug comes out from the system: diffusion and erosion. If the drugs and polymers are vigorous dispersed in the internal structure of solid dispersions, the diffusion of drugs through the matrix will be the chief mechanism. If the drugs and carriers exist in separated particles, then solid dispersion erosion may become the main mechanism for drug release. In some solid dispersion, both mechanisms can manage the drug release at the same time [25].

Carriers Used in Solid Dispersions

Some of the major carriers used in solid dispersion can be described in Table 2.

Methodologies

The core steps involved in the formation of solid dispersion between a drug and polymer are [26]:
1. Transforming drug and polymer from their solid state to fluid or fluid-like state through processes such as melting, dissolving in solvent or cosolvent, or subliming.
2. Mixing the components in their fluid state.
3. Transforming the fluid mixture into solid phase through processes such as congealing, solvent removal, and condensation of sublimed mixture.

Basically, there are various methods for preparation of solid dispersions which can be classified as under:

Melting Method

Because of the toxicity and environmental problems associated with the use of organic solvents, the use the fusion method represents an advantageous means in Preparation of SD when the drug is stable Thermal. However, its use is inappropriate when their polymorphism due to transition that may occur during fusion between the polymorphic forms [27,28]. In this method, the drug and carrier are heated the temperature slightly above its melting point, and the drug is incorporated into the molten carrier. The system remains under heating to obtain a solution homogeneous, macro and microscopically. Posteriorly, the system is cooled under constant stirring. In this case, there is a greater possibility of breaking the crystalline state of the drug to the amorphous state due to the use of high temperatures. However, the possibility of Miscibility is halfway between drug and carrier due to the high viscosity of the polymer in the molten state, in addition, degradation of labile drugs [29].

When the drug has a high solubility the carrier, it can remain "dissolved" in the state solid, originated what is known as a solid solution. Under these conditions, the reduction in particle size provides a peak molecular dispersion of the drug the carrier [30].

Solvent Method

In this method, also known as method coevaporation, the drug and carrier are solubilized Common organic solvent which is then evaporated with constant stirring, yielding a dry residue and solid. Solvent removal can be performed in vacuum rotaevaporator or in a lyophilizer. This method many It is sometimes confused with the co - precipitation; However, in this case, the drug and polymer are dissolved, and subsequently, precipitation is induced by adding a cosolvent. The nature of the solvent and its rate and temperature evaporation are particularly critical in this method. At the same time, the main
disadvantage of this method is the use of organic solvents and the formation of residues, despite being a simple, inexpensive and used in laboratory scale, in addition to the difficulty of selecting a common solvent to dissolve the drug with hydrophobic characteristics and hydrophilic carrier [18].

**Fusion Solvent Method**

In this method, the polymer is heated to slightly above its melting point and the drug, previously solubilized in organic solvent, it is incorporated into the molten carrier. Subsequently, the system is cooled under constant agitation for dry lyophilization, if necessary. This method becomes useful for drugs that have a high melting point or thermolabile [31].

**Kneading Method**

In this method, the polymer and drug are mixed by geometric dilution. The mixture is malaxada with adding the amount of solvent minima (equivalent to 30% of the post of weight) in order to obtain a moist consistency. Industrially, a mixture of components is performed in a malaxadora, and in this case, required some adjustments in the methodology used, initially at the level bench, which can cause some modifications of the physical and chemical characteristics and pharmacotechnical the product. The drying of the material can be done in an oven or directly in malaxadora followed by pulverization to standardize the size particle. Due to the simplicity, the high throughput and the scale transposition facility, this method is the most widely used in the pharmaceutical industry [32].

**Spray Dried Atomization**

This technique has the same principles as the method solvent which, as well as other techniques that have been developed differs only in the way of drying solvent, to produce different characteristics of products obtained. In this case, the process produces SD particles with reduced size and amorphous, with high rate dissolution and minimal residual solvent in the systems, and the possibility of industrial implementation [33]. Although the spray drying technique is one technology that requires high investments in facilities and operations, there are many reasons why the same is widely used, despite the cost. It has recently been used mainly in increasing the class of drugs bioavailability Biopharmaceutical II (low solubility and high permeability), resulting in products with better Functional properties, such as particle size, compaction and dissolution rate [33,34]. For drugs of this class, solubility is the limiting factor of absorption and data and *In vitro* studies may be useful [35]. The advantages related to this technique include producing particles of consistent quality, easy compared to continued use, applicability of the technique both in sensitive material and heat resistant and ability to process various types of raw materials, production of sustained release systems, and increase water solubility of drugs [36].

**Supercritical Fluid Technology**

The process of supercritical fluid has emerged as an alternative method to the solvent method, forming small particle size precipitation and low organic matter content, with also better flow. Powder flowability is important when commercialization of the process is desired [37]. Carbon dioxide is currently we used this technique due to the advantages associated with its use, as a non - toxic gas, non - flammable, inexpensive and low critical temperature, making it attractive in the processing of heat sensitive drugs and the process solvent removal extremely controlled [18]. Although the results promising described in the literature, is a technique still Experimental and having an initial cost very high [38].

**Characterization for Solid Dispersion**

Several different molecular structures of the drug in the matrix can be encountered in solid dispersions. Several techniques have been available to investigate the molecular arrangement in solid dispersions. However, most effort has been put into differentiate between amorphous and crystalline material. Many techniques are available which detect the amount of crystalline material in the dispersion [39].

**Powder X-Ray Diffraction**
Powder X-ray diffraction can be used to qualitatively detect material with long range order. Sharper diffraction peaks indicate more crystalline material [40].

**Infrared Spectroscopy (IR)**

Infrared spectroscopy (IR) can be used to detect the variation in the energy distribution of interactions between drug and matrix. Sharp vibrational bands indicate crystallinity. Fourier Transformed Infrared Spectroscopy (FTIR) was used to accurately detect crystallinity ranging from 1 to 99% in pure material [41].

**Water Vapour Sorption**

Water vapour sorption can be used to discriminate between amorphous and crystalline material when the hygroscopicity is different [42]. This method requires accurate data on the hygroscopicity of both completely crystalline and completely amorphous samples.

**Isothermal Microcalorimetry**

Isothermal microcalorimetry measures the crystallization energy of amorphous material that is heated above its glass transition temperature (Tg) [43]. This technique has some limitations. Firstly, this technique can only be applied if the physical stability is such that only during the measurement crystallization takes place. Secondly, it has to be assumed that all amorphous material crystallizes. Thirdly, in a binary mixture of two amorphous compounds a distinction between crystallization energies of drug and matrix is difficult.

**Dissolution Calorimetry**

Dissolution calorimetry measures the energy of dissolution, which is dependent on the crystallinity of the sample [44]. Usually, dissolution of crystalline material is endothermic, whereas dissolution of amorphous material is exothermic.

**Macroscopic Techniques**

Macroscopic techniques that measure mechanical properties that are different amorphous and crystalline material can be indicative for the degree of crystallinity. Density measurements and Dynamic Mechanical Analysis (DMA) determine the modulus of elasticity for and viscosity and thus affected by the degree of crystallinity. However, also these techniques require knowledge about the additivity of these properties in intimately mixed binary solids [45].

**Differential Scanning Calorimetry (DSC)**

Frequently used technique to detect the amount of crystalline material is Differential Scanning Calorimetry (DSC) [46]. In DSC, samples are heated with a constant heating rate and the amount of energy necessary for that is detected. With DSC the temperatures at which thermal events occur can be detected. Thermal events can be a glass to rubber transition, (re)crystallization, melting or degradation. Furthermore, the melting- and (re)crystallization energy can be quantified. The melting energy can be used to detect the amount of crystalline material.

**Confocal Raman Spectroscopy**

Confocal Raman Spectroscopy is used to measure the homogeneity of the solid mixture. It is described that a standard deviation in drug content smaller than 10% was indicative of homogeneous distribution. Because of the pixel size of 2 µm³, uncertainty remains about the presence of nano-sized amorphous drug particles [47].

**Temperature Modulated Differential Scanning Calorimetry (TMDSC)**

Temperature Modulated Differential Scanning Calorimetry (TMDSC) can be used to assess the degree of mixing of an incorporated drug. Due to the modulation, reversible and irreversible events can be separated. For example, glass transitions (reversible) are separated from crystallization or relaxation (irreversible) in amorphous materials. Furthermore, the value of the Tg is a function of the composition of the homogeneously mixed solid dispersion. It has been shown that the sensitivity of TMDSC is higher than conventional DSC [48]. Therefore, this technique can be used to assess the amount of molecularly dispersed drug [49]. And from that the fraction of drug that is dispersed as separate molecules is calculated [50].
**In vitro Dissolution Studies**

**In vitro** dissolution studies are done for the find out dissolution behavior. The in-vitro dissolution study can be used to demonstrate the bioavailability or bioequivalence of the drug product through **in vitro – in vivo** correlation (IVIVC). On the other hand, if absorption of the drug is dissolution rate limited that means the drug in the gastrointestinal fluid passes freely through the bio-membranes at a rate higher than it dissolves or is released from the dosage form. The specifically designed in-vivo dissolution study will be required in solid dispersion system to access the absorption rate, and hence its bioavailability and to demonstrate the bioequivalence ultimately [51].

**Marketed Products**

Application of solid dispersions is not only restricted to laboratory scale but commercial scale as well. There are numerous marketed formulations available in the market which is shown in Table 3.

**Patents**

Some of the most common patents linked with solid dispersion have been compiled in Table 4 as followed:

**Future Prospects**

The most recurrent apprehensions with solid dispersions have been the capability to scale up the manufacturing technique, the physical steadiness of the dispersion, and the quantity of carrier desirable to simplify the compulsory upsurge in the discharge rate. When a greater amount of carrier/drug ratio is added to a solution, the quantity of dispersion essential to control the usual dose of the drug might be too great to yield a tablet or capsule that could be definitely swallowed easily. The greater the unit dose of the drug, the more probable this difficult situation is to occur. Additional feature that must be reflected is the association amongst **in vitro** and **in vivo** results. Dispersions with a fast-**in vitro** discharge rate might fail to progress with the oral bioavailability if the **in vitro** test situations do not sufficiently simulate the gastrointestinal conditions, or if there is some precise amount

Midha K, et al. *Int J Pharm Pharmacol* of interaction between the carrier and a constituent of the GI. Numerous produces comprising SD are at present on the market and the amount is estimated to intensify radically in the upcoming years.

**References**


37. Chaudhari SP, Dave RH. To prepare and characterize microcrystalline cellulose granules using water and isopropyl alcohol as granulating agents and determine its end-point by thermal and rheological tools. Drug Dev Ind Pharm;2015; 41: 744-752.

52. Compositions and uses thereof provided are solid dispersions, solid molecular complexes, salts and crystalline polymorphs involving propane-1-sulfonic acid \{3-[5-(3-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2, US 20160355513 A1.

53. Solid dispersions of insoluble drug and preparation method there of the present invention relates to a solid dispersion characterized in that it comprises carbamic acid: Myoung Ki Baek, AugustinPegan. US 20160346258.


55. Bendamustine solid dispersions and continuous infusion. Provided herein are pharmaceutical compositions comprising nitrogen mustard, for example bendamustine hydrochloride, solid dispersions substantially free of degradants: Vasilios Voudouris. US 20160310422


57. Solid dispersions containing an apoptosis-inducing agent, Nathaniel Catron: David Lindley, Jonathan M. Miller, Eric A. Schmitt, Ping Tong. US 20150157639 A1

58. Solid dispersions comprising tacrolimus: Per Holm. US 20130189318 A1


63. Solid dispersions of a erb2 (her2) inhibitor: David Shank Fry, Christopher M. Lindemann, Michael Preigh, Corey Jay Bloom, Christopher Donovan Craig, Devon Brevard Dubose, Jeff gautschi, Dan Smithey. US 20140296267 A1

64. Solid retard formulations based on solid dispersions: Gunther Berndl, Juergen Weis, Dietrich Granzow, Bernd Liepold, Ute Lander, Ulrich Westedt, Weniger. US 20140296336 A1


66. Solid dispersion compositions of tebufelone: Gary R. Kelm, Douglas J. Dobrozsi. US 5281420 A

67. Controlled release flutamide composition: Elliot Stupak, W. Philip Cho. US 5162117 A

68. Nifedipine-containing solid preparation composition: HiroitsuKawata, Tadayoshi Ohmura, Katsuhiko Yano, Mikio Matsumura, Saburo Higuchi, Yoshiaki Soeishi, Weniger. US 4412986 A

69. Solid particle dispersion filter dyes for photographicompositions: Donald R. Diehl, Ronda E. Factor. US 4940654 A

70. Anhydrous solid dispersion containing organo flourinated hydrocarbon compounds and its use in cosmetics: Dolores Miguel. US 5830444 A

71. Process for the preparation of a solid dispersion of at least one polyhydric alcohol in a fatty body and the resulting dispersion for cosmetic and

pharmaceutical use: Jean-Claude Ser, Dolores Miguel. US 5437859 A
72. Controlled Release Preparation: Ryoichi Morita, Mitsutoshi Arahira, Ritsuko Honda, Yoshihito Takahashi. US 6156343 A.
74. Solid dispersion composition of FR-900506 substance: Yoshio Ueda, Fumio Shimojo, Yasuo Shimazaki, Kazutake Kado, Toshiyasu Honbo. US 6254889 A.
91. Solid dispersions of a erb2 (her2) inhibitor: David Shank Fry, Christopher M. Lindemann, Michael Preigh, Corey Jay Bloom, Christopher Donovan Craig, Devon Brevard Dubose, Jeff Gautschi, Dan Smity. US 20140296267 A1.

Table 1: Types of solid dispersions

<table>
<thead>
<tr>
<th>Solid Dispersion Type</th>
<th>Remarks</th>
<th>No. of Phases</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Eutectics</td>
<td>The first type of Solid Dispersion prepared</td>
<td>2</td>
</tr>
<tr>
<td>II. Amorphous precipitation in crystalline matrix</td>
<td>Rarely encountered</td>
<td>2</td>
</tr>
<tr>
<td>III. Solid Solutions</td>
<td>Various types are as follows</td>
<td></td>
</tr>
<tr>
<td>Category</td>
<td>Example of carrier</td>
<td></td>
</tr>
<tr>
<td>-------------------------------</td>
<td>-----------------------------------------------------------------------------------</td>
<td></td>
</tr>
<tr>
<td>Superdisintegrants</td>
<td>Calcium silicate, Sodium starch glycolate, Croscarmellosesodium, Cross-linked alginic acid, Cross-linked polyvinylpyrrolidone, Gellan gum, Xanthan gum</td>
<td></td>
</tr>
<tr>
<td>Polymers</td>
<td>Polyethylene glycols, Hydroxypropylmethylcellulose, Polyvinyl pyrrolidone, Polyvinylpolypyrrolidone, Polyvinyl alcohol, Hydroxypropyl cellulose, Poly (2-hydroxyethylmethacrylate), Methacrylic copolymers (Eudragit® S100 sodium salts and Eudragit® L100 sodium salts)</td>
<td></td>
</tr>
<tr>
<td>Carbohydrates</td>
<td>Lactose, Soluble starch, Sorbitol, Mannitol, β-(1-4)-2-amino-2-deoxy-D-glucose Chitosan, Maltose, Galactose, Xylitol, Galactomannan, British gum, Amylodextrin</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2: Types of carriers used in solid dispersions**
Surfactants  | Sorbitan esters (Spans), Polyoxyethylenesterates, Poly (beta-benzyl-L-aspartate)-b- poly (ethyleneoxide), Poly (caprolactone)-b- poly (ethylene oxide), Poloxamers (Lutrol® F 127, Lutrol® F 68), Polyglycolizedglyceride (Labrasol), Polyoxyethylenesorbitan monoesters (Tweens)
---|---
Cyclodextrin  | β-Cyclodextrins, Hydroxypropyl-β-cyclodextrins
Acids  | Citric acid, Succinic acid, Phosphoric acid
Polyglycolized glycerides  | Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
Hydrotropes  | Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxy benzoate, Sodium-phydroxybenzoate, Sodium citrate
Miscellaneous  | Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk, Microcrystalline cellulose, Di calcium phosphate, Silica gel, Sodium chloride, Skimmed milk Microcrystalline cellulose

<table>
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<tr>
<th>S. No.</th>
<th>Application</th>
<th>Example</th>
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<tbody>
<tr>
<td>1</td>
<td>Orodispersible tablets (ODT)</td>
<td>Acelofenac, Indomethacin, Promethazine Hydrochloride</td>
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<tr>
<td>2</td>
<td>Mouth dissolving tablet (MDT)</td>
<td>Celecoxib, Oxcarbazepine</td>
</tr>
<tr>
<td>3</td>
<td>Dissolution rate enhancement</td>
<td>Celecoxib, Hydrocortisone, Ibuprofen, Diazepam</td>
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<tr>
<td>4</td>
<td>Matrix tablets</td>
<td>Indomethacin</td>
</tr>
<tr>
<td>5</td>
<td>Controlled release</td>
<td>Diclofenac sodium, Indomethacin, Ketoprofen, Nifedipine.</td>
</tr>
<tr>
<td>6</td>
<td>Mucoadhesive drug delivery</td>
<td>Piroxicam</td>
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<tr>
<td>7</td>
<td>Solubility enhancement</td>
<td>Hydrocortisone, Carbamazepine, 5-Aminosalicylic acid, Curcumin</td>
</tr>
<tr>
<td>8</td>
<td>Dry powder for reconstitution</td>
<td>Etravirine</td>
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<th>S. No</th>
<th>Patent No.</th>
<th>Active Ingredient</th>
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<td>1</td>
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<td>Crystalline polymorphs involving propane-1-sulfonic acid {3-[5-(4-chloro-phenyl)-1H-pyrrolo[2,3-b]pyridine-3-carbonyl]-2,4-difluorophenyl}-amide.</td>
<td>Solid molecular complexes and Salts.</td>
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</tr>
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<p>| 2 | US20160346258A1 | Carbamic acid 3-(4-benzyloxy-phenyl)-isoxazol-5-ylmethyl ester | Water-soluble polymer having a glass transition temperature lower than the melting point of the active ingredient | 53 |
| 3 | US20160339074A1 | 5-tert-butyl-N-[(1R,2S)-1-[(cyclopropylsulfonyl)carbamoyl]-2-ethenylcyclopropyl]-14-methoxy-3,6-dioxo-1,1a,3,4,5,6,9,10,18,19,20,21,22,22a-tetradecahydro8H7,10-methano[cyclopropa][18,19][1,10,3,6]dioxadiazaclononadecino[11,12b]quinoxaline-8-carboxamide | Acetone;SLS;BHA;BHT;Kollidon VA64 | 54 |
| 4 | US20160310422A1 | Comprising nitrogen mustard, for example bendamustine hydrochloride, solid dispersions substantially free of degradants | Bendamustine hydrochloride solid dispersions | 55 |
| 5 | US20150239848A1 | Enzalutamidine | 56 |
| 6 | US20150157639A1 | Herein Derivatives | 57 |
| 7 | US20130189318A1 | Tacrolimus Derivatives | Hydrophilic or water-miscible vehicle | 58 |
| 8 | US20130224301A1 | Hydroxypolymethylcellulose acetate succinate | Hydrophobic active ingredients | 59 |
| 9 | US20130345320A1 | n,n-diethylaminomethyl methacrylate and methyl methacrylate | Hydrophobic active ingredients | 60 |
| 10 | US20140179719A1 | Valganciclovir hydrochloride | Methanol | 61 |
| 11 | US20140187582A1 | Paroxetine mesylate | Methacrylic acid | 62 |</p>
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<th>n4-[(1,2,4]triazolo[1,5-a]pyridin-7-yl)-3-methylphenyl]-n6-(4,4-dimethyl-4,5-dihydrooxazol-2-yl)quinazoline-4,6-diamine</th>
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<td>US 7364752</td>
<td>HIV protease inhibitor</td>
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<td>Tebufelone</td>
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<td>16</td>
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<td>Flutamide</td>
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<td>US 5830444</td>
<td>Organoflourinated hydrocarbon</td>
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<td>US 5437859</td>
<td>Polyhydric alcohol</td>
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<td>US 6156343</td>
<td>Polyvinylalcohol</td>
<td>Trisodium citrate, sodium sulfate and sodium chloride,</td>
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<td>22</td>
<td>US 6254889</td>
<td>Amorphous xanthine derivative</td>
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