Therapeutic Applications of Solid Dispersions

Subjects: Pharmacology & Pharmacy

Contributor: Verônica da Silva Oliveira , Amanda Silva de Almeida , Ingrid da Silva Albuquerque , Fernanda Ílary Costa Duarte , Bárbara Cristina Silva Holanda Queiroz , Attilio Converti , Ádley Antonini Neves de Lima

Solid dispersions (SDs) are a technological strategy to improve the pharmacological potential of natural or synthetic bioactive molecules, due to the increase in its solubility and bioavailability, leading to a possible improvement of its biological activities. In this sense, the review sought to synthesize and critically examine the studies that address SDs with therapeutic applications, evaluated through *in vitro* and/or *in vivo* tests. This bibliographic survey shows the significant therapeutic potential of SDs in the context of the most diverse biological activities. Among these, including *in vitro* and/or *in vivo* antitumor, antiparasitic, antimicrobial, antioxidant, anti-inflammatory or cytoprotective activities, while additional activities, such as gastroprotective, hepatoprotective, antidiabetic or antinociceptive, were highlighted by *in vivo* studies.

Although SDs have already been studied and cited in the literature, the number of studies published with a focus on *in vitro* and *in vivo* trials is still relatively small, considering the great potential of these formulations in pharmaceutical technology and with the most diverse applications. The results of biological activity studies showed that SDs, as a drug release tool, is not a limiting factor for the execution of *in vitro* and *in vivo* tests. Additionally, it stands out as a promising system in which the active principle and the carrier interact, allowing, in most cases, an increase in the pharmacological potential due to changes in the physicochemical properties of the constituents. Thus, SDs can represent a safe and effective alternative for the development and improvement of drugs directed to a wide range of pharmacological treatments.

solid dispersions drug delivery biological applications

1. Introduction

Many drug candidates have low aqueous solubility, which can make their oral absorption inadequate. According to the literature, approximately 40% of marketed drugs are poorly soluble in water, as are, according to the Biopharmaceutical Classification System, about 40–90% of new drug candidates [1][2][3][4].

The slow dissolution rate and low solubility of some drugs lead to unpredictable bioavailability, non-reproducible clinical response or treatment inefficiency due to low therapeutic plasma levels; therefore, their use must be optimized using formulation strategies capable of improving their administration [5].

Several technological strategies have been developed and employed to circumvent this situation such as complexation with cyclodextrins, particle size reduction by micronization, crystal development, nanotechnology [5], salt formation and solid dispersions (SDs) [6][7]. However, some of these strategies have shown disadvantages

including the development of active forms *in vivo*, high execution cost and considerable levels of toxicity. Some of these limits can be overcome by employing solid dispersions, a viable, well-established and widely-used strategy to increase the dissolution rate and solubility of poorly water-soluble drugs [4][6][7].

SDs can be defined as molecular mixtures of drugs that are not soluble in hydrophilic carriers, which exhibit a drug release profile driven by the polymer properties [8]. The so-called first-generation crystalline SDs, which use crystalline carriers such as urea and sugars including sucrose, dextrose and galactose, have the disadvantage of high thermodynamic stability that prevents a quick release of drugs [9]. In second-generation SDs drugs are dispersed in usually polymeric amorphous carriers [8], while the carriers used in third-generation SDs are surfactants or a mixture of amorphous polymers and surfactants [10].

The use of hydrophilic polymeric matrices to develop SDs for the release of commercial drugs or new drugs candidates has been shown to be a promising alternative able to improve their pharmacokinetic properties [7].

This review deals with SDs, mainly those belonging to the second-generation class that use polymers as carriers. It describes the main *in vitro* and *in vivo* activities (Figure 1) of SDs having different compositions and various preparation methods, intending to innovate and enhance the release of poorly water-soluble drugs, as well as improving the biological activities of the loaded bioactive compounds.

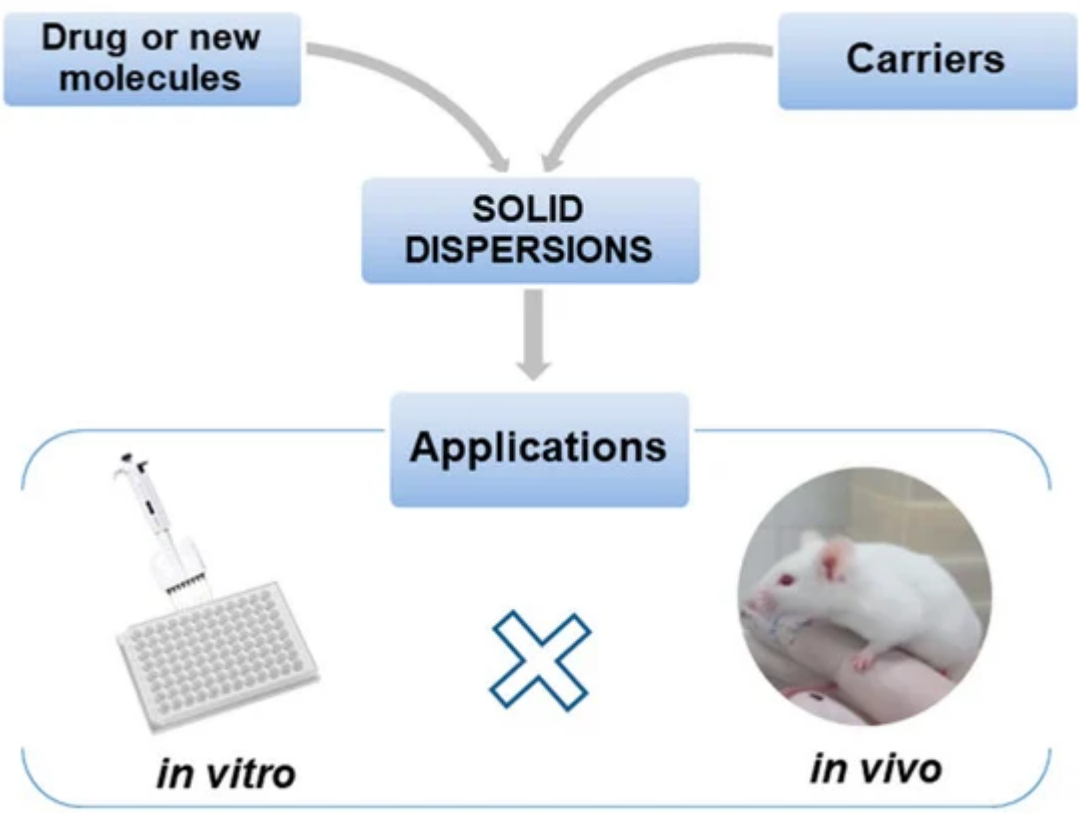

Figure 1. Representation of the application of solid dispersions in biological assays.

2. *In Vitro* Study of Solid Dispersions in Polymeric Matrices

This section deals with solid dispersions (SDs) prepared to improve the properties and release of poorly soluble drugs and drug candidates of natural or synthetic origin. The preparation and use of SDs have been reported in several *in vitro* studies, which have been numerically quantified and classified in Figure 2, based on the biological activities of their active compounds, while the main information on these studies is summarized in Table 1.

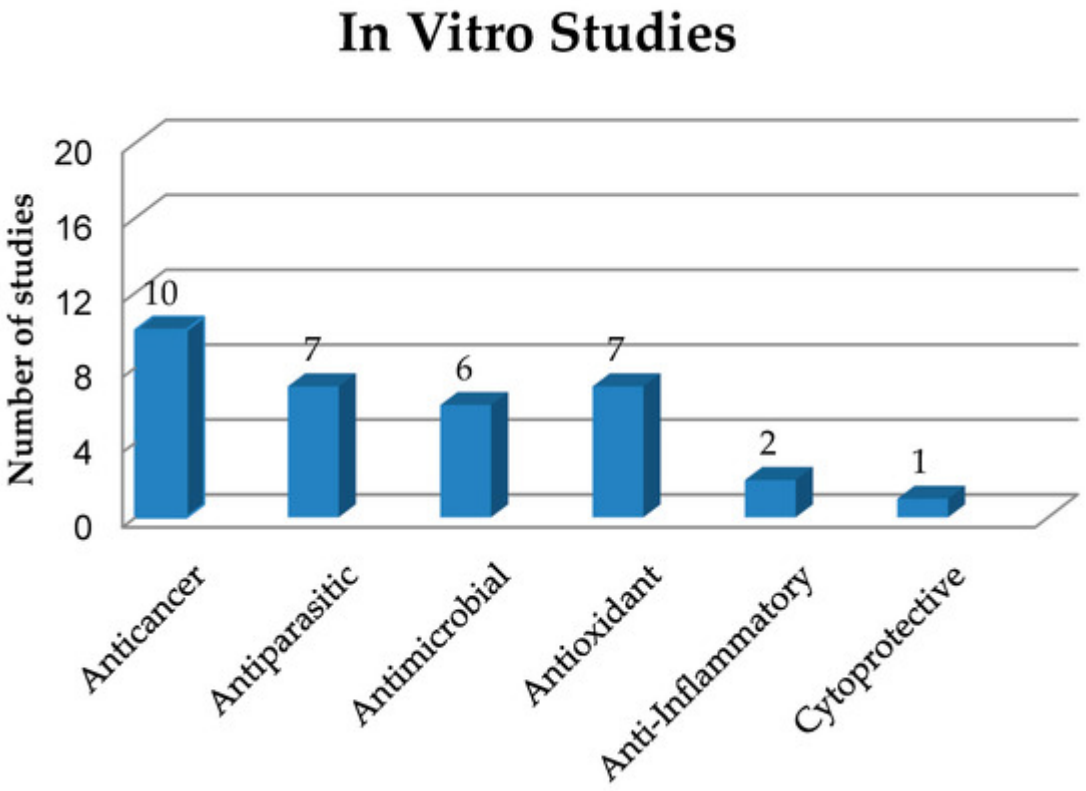

Figure 2. Quantification and classification of *in vitro* studies on solid dispersions published in the period from 2009 to 2020.

Table 1. *In vitro* studies on solid dispersions.

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
OHPP	Niclosamide	PC-3, HeLa, A549	Anticancer	SDs showed higher cytotoxicity to target cells (lower IC50) than the niclosamide solution.	[11]
OHPP	Paclitaxel	PC-3, HeLa, A549	Anticancer	SDs showed significantly higher cytotoxicity to target cells (lower IC50) than the paclitaxel solution.	[12]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
PVP/VA TPGS	Paclitaxel	BT-474, MCF-7, SK-BR-3	Anticancer	SDs showed higher cytotoxicity against cancer cells compared to the pure drug.	[13]
Brij®L4	Chrysin	HT29	Anticancer	The higher solubility of chrysin in SDs compared to water solution increased cytotoxicity.	[14]
Poloxamer 407	Curcumin (CM)	NCIH460, HeLa, HepG2, MCF-7 and PLP2	Anticancer	Anticancer SDs showed cytotoxicity against all tumor cell lines tested, but no toxic effects on non-tumor cells.	[15]
		AChE, BChE, GST, MAO A-B	Enzyme inhibitory /Antioxidant	SD was able to inhibit the activities of AChE, BChE and GST in aqueous medium.	
		LPS-stimulated murine macrophages (RAW 264.7)	Anti-inflammatory	IC50 (inhibitory concentration of 50% NO production by macrophages) > 400 µg/mL.	
PVP K30	Zn(II)-curcumin complex	HepG2, SK-HEP1	Anticancer	SD of Zn(II)-curcumin complex had a potent anticancer effect.	[16]
HPMC, PVP K30, PEG 6000	Telaprevir	HepG2	Anticancer	The antitumor activity was dose dependent and even with the addition of the polymer the drug maintained its efficacy.	[17]
Soluplus ®	Angelica gigas Nakai	HeLa, HEK 293	Anticancer	SD at the concentration of 200 µg/mL showed a significant decrease (to only 17.37%) in cell viability. There was no toxicity to normal cells.	[18]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
Eudragit S-100	Berberine hydrochloride (HB)	SW480, HCT116, Caco-2	Anticancer	The release of HB from SDs was effective and cell viability was reduced in a dose and time dependent manner.	[19]
PVP K30	IIIM-290	Ehrlich ascites carcinoma cells	Cytotoxic	Despite the reduced amount of IIIM-290 in SD, the IC50 value of SD was lower than that of IIIM-290 alone.	[20]
Poloxamer 407	Benznidazole	Epimastigotes of *Trypanosoma cruzi*	Antichagasic	SDs enhanced drug solubility, release kinetics and parasitic activity.	[21]
Low-substituted HPC	Benznidazole	Epimastigotes and intracellular amastigotes of *T. cruzi* (CL-B5)	Antichagasic	SDs had higher antiparasitic activity against amastigotes than epimastigotes.	[22]
Gelucire 50/13	Ursolic acid	Trypomastigotes of *T. cruzi* Y	Antichagasic	Increased antiparasitic activity.	[23]
PVP K30,PVP/VA, Kollidon-CL-M, sodium starch glycolate	Praziquantel	Adult schistosomes of *Schistosoma mansoni*	Antischistosomal	Increased solubility, better bioavailability and stronger antiparasitic activity.	[24]
PVP K30	Praziquantel	Newly transformed schistosomula of *S. mansoni* and adults	Antischistosomal	Increased solubility, reduced dosage especially for children and increased antiparasitic activity	[25]
Soluplus, PEG 400, Lutrol F127 and Lutrol F68	Artemether	Schizonts of *Plasmodium falciparum* 3D7	Antimalarial	Increased dissolution rate, amorphous form, increased solubility and, mainly,	[26]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
				increased antimalarial activity.	
Soluplus, Kollidon VA64, Plasdone S630	Lumefantrine	ITG cells	Antimalarial	Increased antiparasitic activity.	[27]
Chitosan	Abietic acid	*Staphylococcus epidermidis*	Antimicrobial	SD exhibited better MIC values against *S. epidermidis* than chitosan and abietic acid alone.	[28]
		DPPH radical scavenging	Antioxidant	SD had higher antioxidant power (IC50 of 0.61 mg/mL) than abietic acid alone (IC50 of 11 mg/mL).	
PVP K30 and HPMCAS	Griseofulvin	Dermatophytes of *Trichophyton rubrum* NCPF 935	Antimicrobial	SDs significantly reduced biofilm formation when compared to the control.	[29]
Pluronic F127	Gatifloxacin	*Staphylococcus aureus*	Antimicrobial	The gatifloxacin/Pluronic F127 system exhibited antimicrobial efficacy when compared to commercialized eye drops.	[30]
PVP K30	Curcumin	*Salmonella enteritidis*	Antimicrobial	SD had a strong antimicrobial effect on *S. enteritidis*, while CM alone did not show antimicrobial activity *in vitro*	[31]
HPMC	Curcumin	*Escherichia coli*	Antimicrobial	SD used to prepare phototoxic supersaturated solutions showed significant bactericidal activity against *E. coli*.	[32]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
Polaxamer 407	Curcumin	*E. coli*, *Pseudomonas aeruginosa* and *S. aureus*	Antimicrobial	The association between SD and silver nanoparticles increased CM antimicrobial and antioxidant activities.	[33]
		DPPH radical scavenging	Antioxidant		
PVP K25	Quercetin	DPPH radical scavenging	Antioxidant	Increased quercetin antioxidant activity in SD ($0.61 \pm 0.03 \leq IC50 \leq 1.00 \pm 0.02$ µg/mL).	[34]
Mannitol	Coenzyme Q10	Intracellular ROS level	Antioxidant	The SD with the smallest particle size showed the greatest absorption of UVB radiation as well as the highest antioxidant activity *in vitro*.	[35]
PVP K30	Usnic acid	DPPH radical scavenging	Antioxidant	Increased usnic acid solubility and antioxidant activity.	[36]
PEG 4000	Luteolin	DPPH	Antioxidant	Polymers increased luteolin solubility and antioxidant activity.	[37]
PVP K30, PEG 6000 and HPMC	α,β-Amyrin	LPS-stimulated macrophages J774	Anti-inflammatory	SDs enhanced the anti-inflammatory activity of α,β-amyrin.	[7]
HPMC	Curcumin	HepG2	Cytoprotective	SDs showed better cytoprotective activity than pure CM and inhibited cell death induced by t-BHP.	[38]

OHPP, Octenylsuccinate hydroxypropyl phytoglycogen; IC50, Half inhibitory concentration; PVP/VA, Polyvinylpyrrolidone/vinyl acetate; TPGS, D-α-toco-pheryl polyethylene glycol-1000-succinate; PVP, Polyvinylpyrrolidone; SD, Solid dispersion; AChE, Acetylcholinesterase; BChE, Butyrylcholinesterase; CM, Curcumin; GST, Glutathione S-transferase; MAO, Monoamine oxidase; LPS, Lipopolysaccharide; NO, Nitric oxide; PEG, Polyethylene glycol; HPMC, Hydroxypropyl methylcellulose; ITG (chloroquine-resistant cell line); DPPH, 2,2-

diphenyl-1-picryl-hydrazyl-hydrate; HPMCAS, Hydroxypropyl methylcellulose acetate succinate; MIC, Minimum inhibitory concentration; ROS, Reactive oxygen species; t-BHP, tert-Butylhydroperoxide.

3. *In Vivo* Studies of Solid Dispersions in Polymeric Matrices

As already mentioned, solid dispersions (SDs) have been used as a strategy in pharmaceutical technology to circumvent some limitations presented by drugs and new bioactive compounds such as low solubility and bioavailability. In this sense, this section addresses *in vivo* studies on SDs with different biological activities, as shown in Figura 3 and quantitatively expressed in Figure 4 . The main information about these studies is summarized in Table 2.

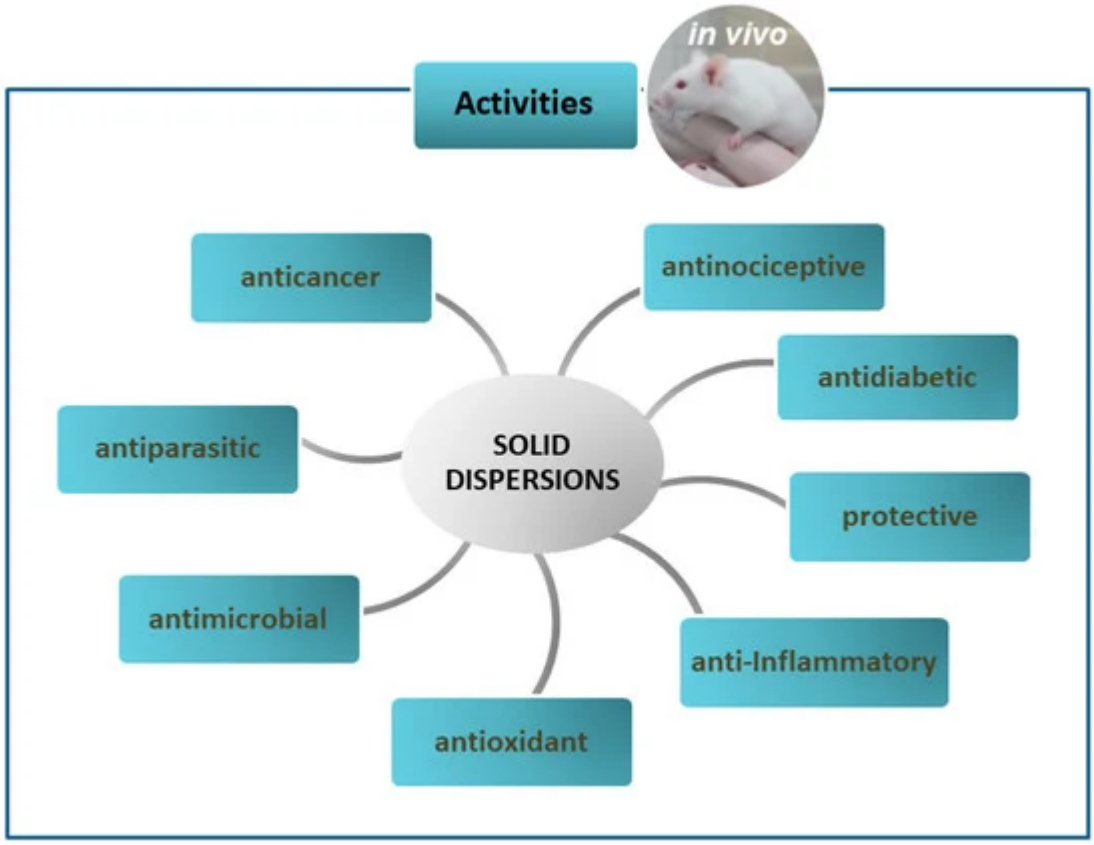

Figure 3. *In vivo* activities of solid dispersions.

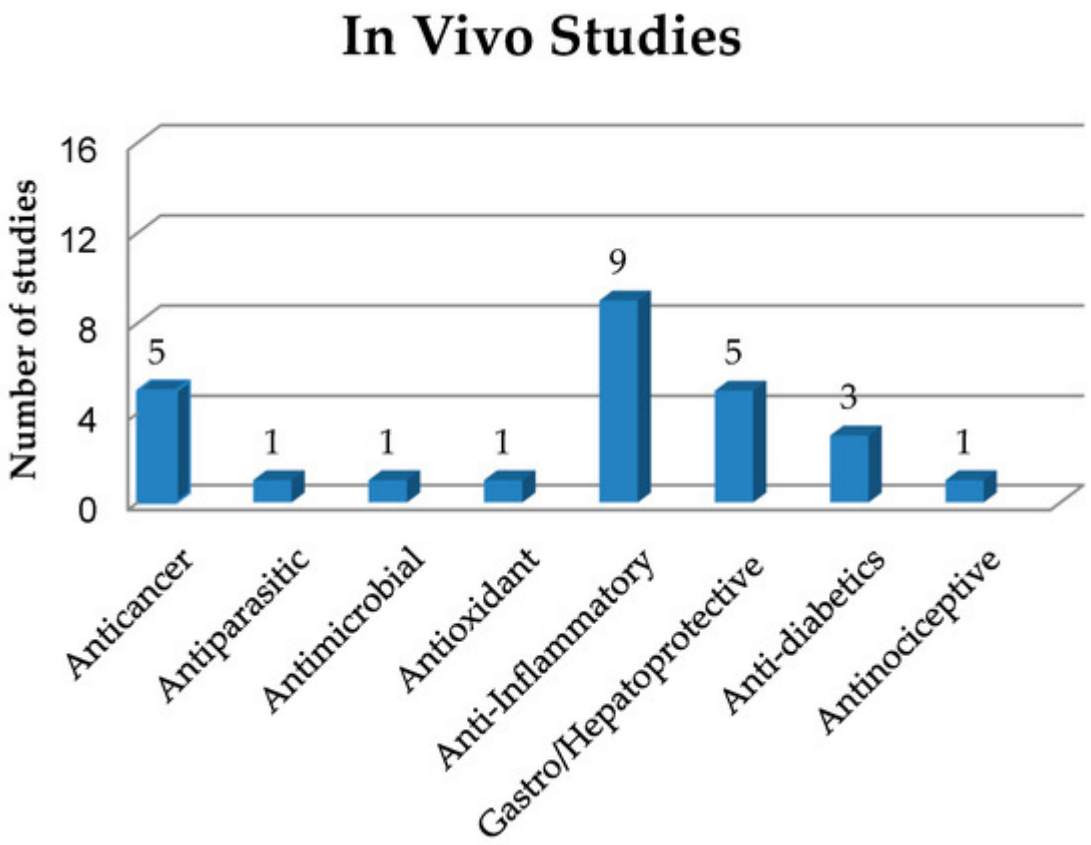

Figure 4. Quantification and classification of *in vivo* studies on solid dispersions published in the period from 2009 to 2020.

Table 2. *In vivo* studies of solid dispersions.

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
PVP K30	IIIM-290	Swiss male mice (18–23 g)	25, 50 and 75 mg/kg	Anticancer	SD was able to reduce the IIIM-290 dose by at least 1.5-fold thanks to its efficiency in Ehrlich solid tumor model.	[20]
Soluplus®	9-Nitrocamptothecin	Male Sprague-Dawley rats (20 ± 2 g)	4 mg/kg	Anticancer	SD showed higher tumor growth inhibitory rate than the pure compound due to improved oral bioavailability.	[39]

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
(+)-Xylitol	(−)-Oleocanthal	Athymic nude mice	10 mg/kg	Anticancer	Treatment with SD showed prevention, lower growth rate and less recurrence of tumor.	[40]
PVP K30	Zinc(II)-curcumin complex	B-NDG, BALB/c mice	100 mg/kg	Anticancer	SD reduced tumor size and weight in animals.	[17]
PVP K30	*Selaginella doederleinii* Hieron	BALB/c mice	200 mg/kg	Anticancer	SD reduced tumor size as well as the level of tumor angiogenesis.	[41]
Low substituted HPC	Benznidazole	Female NMRI mice (25 ± 2 g)	25 mg/kg/day	Antichagasic	The best SD showed a 96.65% trypanocidal activity, expressed as percentage reduction in the area under the parasitic curve.	[22]
PVP K30	Curcumin (CM)	Male Cobb-Vantress broiler chickens	1 g/kg of feed	Antimicrobial	The synergistic effect of 0.05% CM/PVP SD with 0.05% boric acid reduced colonization of *Salmonella enteritidis* in crop and ceca-cecal tonsils.	[31]
PVP K30	Taurine-zinc complex	Female Sprague-Dawley rats (240–260 g)	100 and 200 mg/kg/day	Antioxidant Gastroprotective	SDs protected rat gastric mucosa from ethanol-induced injury and increased SOD activity and	[42]]

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
					glutathione	
Kollidon (VA64)	Triacetylated andrographolide (TA)	Male Kunming mice	50, 100 and 200 mg/kg/day	Anti-inflammatory	TA-SD prepared with VA64 significantly improved the drug activity against ulcerative colitis.	[43]
PVP K30, Poloxamer 188	Curcumin	Female CD-1 mice	100 mg/kg oral doses	Anti-inflammatory	CM-SD prepared with PVP decreased matrix metallo-peptidase 9 expression and levels of IL-1β and IL-6 cytokines.	[44]
Gelucire®50/13-Aerosil®	Curcumin	Rat	10 to 100 mg/kg	Anti-inflammatory	A CM-SD dose of 100 mg/kg was more effective than 5 mg/kg indomethacin in reducing edema	[45]
HPMC, lecithin and isomalt	Curcumin	Male Sprague-Dawley rats	5 mg/kg	Anti-inflammatory	A CM-SD dose of 5 mg/kg had greater anti-inflammatory activity than 50 mg/kg curcumin alone.	[46]
Crospovidone	Aceclofenac	Male Sprague-Dawley rats	1 g/cm2 (topical)	Anti-inflammatory	The enhanced drug permeation increased the intensity of the anti-inflammatory response.	[47]
PEG 8000	Ibuprofen	Wistar rats	20 mg/kg	Anti-inflammatory	All SDs showed better anti-inflammatory activity than the pure drug, allowing up to 90% edema	[48]

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
					inhibition after 6 h.	
Urea and mannitol	Flurbiprofen	Rat	11.69 mg/kg	Anti-inflammatory	SD showed better inhibition of rat paw edema up to 16 h.	[49]
Paracetamol	Meloxicam	Rat	-	Anti-inflammatory	SDs reduced by more than 50% the volume of carrageenan-induced tail edema compared to the physical mixture.	[50]
PVP K30	Chelerythrine (CHE)	Mice	10 mg/kg	Anti-inflammatory	SD enhanced CHE anti-inflammatory effect by reducing the levels of TNF-α, IL-6 and NO in mice serum.	[51]
HPMC	Curcumin	Male BABL/c mice	200 and 400 mg/kg	Hepatoprotective	The best SD increased the hepatoprotective efficacy of CM.	[38]
HPC	Nobiletin	Male Sprague-Dawley rats (220 g)	2 mg of drug/kg	Hepatoprotective	SD was more effective than the crystalline drug in rats with acute liver injury	[52]
PVP K30	Silymarin	Adult male albino rats (150–200 g)	25 mg/kg	Hepatoprotective	The best SD improved biomarker rates and had a significantly better hepatoprotective effect than the commercial extract	[53]

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
PVP K30	Silymarin	Male Sprague-Dawley rats (190–210 g)	50 mg/kg	Hepatoprotective	SD improved drug solubility and hepatoprotective activity, reducing the AST levels.	[54]
Poloxamer 188	Repaglinide	Wistar rats (150–250 g))	(1 mg of drug)	Antihyperglycemic	SD obtained by the microwave method improved the drug anti-hyperglycemic activity.	[55]
Soluplus1 and PEG 4000	Glimepiride	Albino Wistar rats (200–250 g)	0.0285 mg of drug/kg	Anti-diabetic	SD reduced the glucose level in rats more than the pure drug and a commercial product	[5]
PVP K17	Pioglitazone	Male Swiss albino mice (25–30 g)	30 mg/kg SD	Antihyperglycemic	SD reduced the mean glucose level in mice more than the pure drug and a commercial product.	[56]
HPMC	Hecogenin acetate	Male Swiss mice (28–35 g)	40 mg/kg	Antinociceptive	Both the drug alone and its SD with HPMC-reduced mechanical and thermal hyperalgesia induced by crushing of the sciatic nerve in mice.	[57]

technologies for poorly water-soluble drug delivery—An update. Int. J. Pharm. 2018, 535, 379–392.

3. Loftsson, T.; Brewster, M.E. Pharmaceutical applications of cyclodextrins: Basic science and product development. J. Pharm. Pharmacol. 2010, 62, 1607–1621.
4. Worku, Z.A.; Aarts, J.; Singh, A.; Mooter, G.V.D. Drug–Polymer Miscibility across a Spray Dryer: A Case Study of Naproxen and Miconazole Solid Dispersions. Mol. Pharm. 2014, 11, 1094–1101.
5. Reginald-Opara, J.N.; Attama, A.; Ofokansi, K.; Umeyor, C.; Kenechukwu, F. Molecular interaction between glimepiride and Soluplus®-PEG 4000 hybrid based solid dispersions: Characterisation and anti-diabetic studies. Int. J. Pharm. 2015, 496, 741–750.

6. Danda, L.J.D.A.; Batista, L.D.M.; Melo, V.C.S.; Sobrinho, J.L.S.; Soares, M.F.D.L.R. Combining amorphous solid dispersions for improved kinetic solubility of posaconazole simultaneously released from soluble PVP/VA64 and an insoluble ammonio methacrylate copolymer. Eur. J. Pharm. Sci. 2019, 133, 79–85.
7. Júnior, W.F.D.S.; Pinheiro, J.G.D.O.; De Menezes, D.L.B.; Silva, N.E.D.S.E.; De Almeida, P.D.O.; Lima, E.S.; Veiga-Junior, V.F.; De Azevedo, E.P.; Lima, E.S. Development, Physicochemical Characterization and In Vitro Anti-Inflammatory Activity of Solid Dispersions of α,β Amyrin Isolated from Protium Oilresin. Molecules 2017, 22, 1512.
8. Vasconcelos, T.; Sarmento, B.; Costa, P.C. Solid dispersions as strategy to improve oral bioavailability of poor water soluble drugs. Drug Discov. Today 2007, 12, 1068–1075.
9. Leuner, C. Improving drug solubility for oral delivery using solid dispersions. Eur. J. Pharm. Biopharm. 2000, 50, 47–60.
10. Zhang, Z.; Chen, Y.; Deng, J.; Jia, X.-B.; Zhou, J.; Lv, H. Solid dispersion of berberine–phospholipid complex/TPGS 1000/SiO2: Preparation, characterization and in vivo studies. Int. J. Pharm. 2014, 465, 306–316.
11. Xie, Y.; Yao, Y. Octenylsuccinate hydroxypropyl phytoglycogen enhances the solubility and in-vitro antitumor efficacy of niclosamide. Int. J. Pharm. 2018, 535, 157–163.
12. Xie, Y.; Yao, Y. Incorporation with Dendrimer-Like Biopolymer Leads to Improved Soluble Amount and In Vitro Anticancer Efficacy of Paclitaxel. J. Pharm. Sci. 2019, 108, 1984–1990.
13. Choi, J.-S.; Cho, N.H.; Kim, D.-H.; Park, J.-S. Comparison of paclitaxel solid dispersion and polymeric micelles for improved oral bioavailability and in vitro anti-cancer effects. Mater. Sci. Eng. C 2019, 100, 247–259.
14. Lee, S.H.; Lee, Y.-S.; Song, J.G.; Han, H.-K. Improved In vivo Effect of Chrysin as an Absorption Enhancer Via the Preparation of Ternary Solid Dispersion with Brij®L4 and Aminoclay. Curr. Drug Deliv. 2018, 16, 86–92.
15. De Sá, I.S.; Peron, A.P.; Leimann, F.V.; Bressan, G.N.; Krum, B.N.; Fachinetto, R.; Pinela, J.; Calhelha, R.C.; Barreiro, M.F.; Ferreira, I.C.; et al. In vitro and in vivo evaluation of enzymatic and antioxidant activity, cytotoxicity and genotoxicity of curcumin-loaded solid dispersions. Food Chem. Toxicol. 2019, 125, 29–37.
16. Wu, R.; Mei, X.; Ye, Y.; Xue, T.; Wang, J.; Sun, W.; Lin, C.; Xue, R.; Zhang, J.; Xu, D. Zn(II)-curcumin solid dispersion impairs hepatocellular carcinoma growth and enhances chemotherapy by modulating gut microbiota-mediated zinc homeostasis. Pharmacol. Res. 2019, 150, 104454.
17. Xiong, X.; Zhang, M.; Hou, Q.; Tang, P.; Suo, Z.; Zhu, Y.; Li, H. Solid dispersions of telaprevir with improved solubility prepared by co-milling: Formulation, physicochemical characterization and cytotoxicity evaluation. Mater. Sci. Eng. C 2019, 105, 110012.

18. Jiang, Y.; Piao, J.; Cho, H.-J.; Kang, W.-S.; Kim, H. Improvement in antiproliferative activity of Angelica gigas Nakai by solid dispersion formation via hot-melt extrusion and induction of cell cycle arrest and apoptosis in HeLa cells. Biosci. Biotechnol. Biochem. 2015, 79, 1635–1643.
19. Guo, S.; Wang, G.; Wu, T.; Bai, F.; Xu, J.; Zhang, X. Solid dispersion of berberine hydrochloride and Eudragit® S100: Formulation, physicochemical characterization and cytotoxicity evaluation. J. Drug Deliv. Sci. Technol. 2017, 40, 21–27.
20. Kumar, V.; Mintoo, M.J.; Mondhe, D.M.; Bharate, S.B.; Vishwakarma, R.A.; Bharate, S.S. Binary and ternary solid dispersions of an anticancer preclinical lead, IIIM-290: In vitro and in vivo studies. Int. J. Pharm. 2019, 570, 118683.
21. Simonazzi, A.; Davies, C.; Cid, A.G.; Gonzo, E.; Parada, L.; Bermúdez, J.M. Preparation and Characterization of Poloxamer 407 Solid Dispersions as an Alternative Strategy to Improve Benznidazole Bioperformance. J. Pharm. Sci. 2018, 107, 2829–2836.
22. Fonseca-Berzal, C.; Palmeiro-Roldán, R.; Escario, J.A.; Torrado, S.; Arán, V.J.; Torrado-Santiago, S.; Gómez-Barrio, A. Novel solid dispersions of benznidazole: Preparation, dissolution profile and biological evaluation as alternative antichagasic drug delivery system. Exp. Parasitol. 2015, 149, 84–91.
23. Eloy, J.O.; Saraiva, J.; De Albuquerque, S.; Marchetti, J.M. Solid Dispersion of Ursolic Acid in Gelucire 50/13: A Strategy to Enhance Drug Release and Trypanocidal Activity. AAPS PharmSciTech 2012, 13, 1436–1445.
24. Perissutti, B.; Passerini, N.; Trastullo, R.; Keiser, J.; Zanolla, D.; Zingone, G.; Voinovich, D.; Albertini, B. An explorative analysis of process and formulation variables affecting comilling in a vibrational mill: The case of praziquantel. Int. J. Pharm. 2017, 533, 402–412.
25. Albertini, B.; Perissutti, B.; Bertoni, S.; Zanolla, D.; Franceschinis, E.; Voinovich, D.; Lombardo, F.; Keiser, J.; Passerini, N. Combining Mechanochemistry and Spray Congealing for New Praziquantel Pediatric Formulations in Schistosomiasis Treatment. Int. J. Mol. Sci. 2019, 20, 1233.
26. Fule, R.A.; Meer, T.A.; Sav, A.R.; Amin, P. Artemether-Soluplus Hot-Melt Extrudate Solid Dispersion Systems for Solubility and Dissolution Rate Enhancement with Amorphous State Characteristics. J. Pharm. 2013, 2013, 1–15.
27. Fule, R.; Meer, T.; Sav, A.; Amin, P. Solubility and dissolution rate enhancement of lumefantrine using hot melt extrusion technology with physicochemical characterisation. J. Pharm. Investig. 2013, 43, 305–321.
28. Crucitti, V.C.; Migneco, L.M.; Piozzi, A.; Taresco, V.; Garnett, M.; Argent, R.H.; Francolini, I. Intermolecular interaction and solid state characterization of abietic acid/chitosan solid

dispersions possessing antimicrobial and antioxidant properties. Eur. J. Pharm. Biopharm. 2018, 125, 114–123.

29. Al-Obaidi, H.; Kowalczyk, R.M.; Kalgudi, R.; Zariwala, M.G. Griseofulvin solvate solid dispersions with synergistic effect against fungal biofilms. Colloids Surfaces B Biointerfaces 2019, 184, 110540.
30. Kanoujia, J.; Kushwaha, P.S.; Saraf, S.A. Evaluation of gatifloxacin pluronic micelles and development of its formulation for ocular delivery. Drug Deliv. Transl. Res. 2014, 4, 334–343.
31. Hernandez-Patlan, D.; Solis-Cruz, B.; Pontin, K.P.; Latorre, J.D.; Baxter, M.F.A.; Hernandez-Velasco, X.; Merino-Guzman, R.; Méndez-Albores, A.; Hargis, B.M.; Lopez-Arellano, R.; et al. Evaluation of a Solid Dispersion of Curcumin With Polyvinylpyrrolidone and Boric Acid Against Salmonella Enteritidis Infection and Intestinal Permeability in Broiler Chickens: A Pilot Study. Front. Microbiol. 2018, 9, 1289.
32. Hegge, A.B.; Vukićević, M.; Bruzell, E.; Kristensen, S.; Tønnesen, H. Solid dispersions for preparation of phototoxic supersaturated solutions for antimicrobial photodynamic therapy (aPDT). Eur. J. Pharm. Biopharm. 2013, 83, 95–105.
33. Alves, T.; Chaud, M.; Grotto, D.; Jozala, A.F.; Pandit, R.; Rai, M.; Dos Santos, C.A. Association of Silver Nanoparticles and Curcumin Solid Dispersion: Antimicrobial and Antioxidant Properties. AAPS PharmSciTech 2017, 19, 225–231.
34. Costa, A.R.D.M.; Marquiafável, F.S.; Vaz, M.M.D.O.L.L.; Rocha, B.A.; Bueno, P.C.P.; Amaral, P.L.M.; Barud, H.D.S.; Berreta-Silva, A.A. Quercetin-PVP K25 solid dispersions. J. Therm. Anal. Calorim. 2010, 104, 273–278.
35. Ge, Y.; Zhao, X.; Wang, S.; Zu, Y.; Zhao, T.; Sang, M.; Sui, X.; Wang, K. 10 (CoQ10) Prepared by Heat Melt and High-pressure Homogenization Method. Curr. Nanosci. 2014, 10, 292–296.
36. Fitriani, L.; Rismawati, E.; Umar, S.; Zaini, E. Solid dispersion of usnic acid-PVP K30 and evaluation of antioxidant activity. Rasayan J. Chem. 2018, 11, 1643–1648.
37. Alshehri, S.; Imam, S.S.; Altamimi, M.A.; Hussain, A.; Shakeel, F.; Elzayat, E.M.; Mohsin, K.; Ibrahim, M.; Alanazi, F. Enhanced Dissolution of Luteolin by Solid Dispersion Prepared by Different Methods: Physicochemical Characterization and Antioxidant Activity. ACS Omega 2020, 5, 6461–6471.
38. Shin, M.-S.; Yu, J.S.; Lee, J.; Ji, Y.S.; Joung, H.J.; Han, Y.-M.; Yoo, H.H.; Kang, K.; Shin, Y. A Hydroxypropyl Methylcellulose-Based Solid Dispersion of Curcumin with Enhanced Bioavailability and its Hepatoprotective Activity. Biomolecules 2019, 9, 281.
39. Lian, X.; Dong, J.; Zhang, J.; Teng, Y.; Lin, Q.; Fu, Y.; Gong, T. Soluplus® based 9-nitrocamptothecin solid dispersion for peroral administration: Preparation, characterization, in vitro and in vivo evaluation. Int. J. Pharm. 2014, 477, 399–407.

40. Qusa, M.H.; Siddique, A.B.; Nazzal, S.; El Sayed, K. Novel olive oil phenolic (−)-oleocanthal (+)-xylitol-based solid dispersion formulations with potent oral anti-breast cancer activities. Int. J. Pharm. 2019, 569, 118596.
41. Chen, B.; Wang, X.; Zhang, Y.; Huang, K.; Liu, H.; Xu, D.; Li, S.; Liu, Q.; Huang, J.; Yao, H.; et al. Improved solubility, dissolution rate and oral bioavailability of main biflavonoids from Selaginella doederleinii extract by amorphous solid dispersion. Drug Deliv. 2020, 27, 309–322.
42. Yu, C.; Mei, X.-T.; Zheng, Y.-P.; Xu, D. Gastroprotective effect of taurine zinc solid dispersions against absolute ethanol-induced gastric lesions is mediated by enhancement of antioxidant activity and endogenous PGE2 production and attenuation of NO production. Eur. J. Pharmacol. 2014, 740, 329–336.
43. Gou, J.; Fei, S.; Xue, B.; Zhang, J.; Zhang, Y.; Wang, X.; Zhang, Y.; Yin, T.; He, H.; Tang, X. Triacetylated andrographolide solid dispersions: Preparation, stability study and in vivo anti-inflammation in mice ulcerative colitis model. J. Drug Deliv. Sci. Technol. 2019, 51, 91–100.
44. He, Y.; Liu, H.; Bian, W.; Liu, Y.; Liu, X.; Ma, S.; Zheng, X.; Du, Z.; Zhang, K.; Ouyang, D. Molecular Interactions for the Curcumin-Polymer Complex with Enhanced Anti-Inflammatory Effects. Pharmaceutics 2019, 11, 442.
45. Teixeira, C.C.C.; Mendonça, L.M.; Bergamaschi, M.M.; Queiroz, R.H.C.; Souza, G.E.P.; Antunes, L.M.G.; Freitas, L. Microparticles Containing Curcumin Solid Dispersion: Stability, Bioavailability and Anti-Inflammatory Activity. AAPS PharmSciTech 2015, 17, 252–261.
46. Chuah, A.M.; Jacob, B.; Jie, Z.; Ramesh, S.; Mandal, S.; Puthan, J.K.; Deshpande, P.; Vaidyanathan, V.V.; Gelling, R.W.; Patel, G.; et al. Enhanced bioavailability and bioefficacy of an amorphous solid dispersion of curcumin. Food Chem. 2014, 156, 227–233.
47. Jana, S.; Ali, S.A.; Nayak, A.K.; Sen, K.K.; Basu, S.K. Development of topical gel containing aceclofenac-crospovidone solid dispersion by “Quality by Design (QbD)” approach. Chem. Eng. Res. Des. 2014, 92, 2095–2105.
48. Kenechukwu, F.C.; Ofokansi, K.C.; Ezugwu, R.O.; Attama, A.A. Improved dissolution and anti-inflammatory activity of ibuprofen-polyethylene glycol 8000 solid dispersion systems. Int. J. Pharm. Investig. 2016, 6, 139–147.
49. Malipeddi, V.R.; Dua, K.; Awasthi, R. Development and characterization of solid dispersion-microsphere controlled release system for poorly water-soluble drug. Drug Deliv. Transl. Res. 2016, 6, 540–550.
50. Al-Remawi, M.; Ali, A.M.A.; Khames, A.; Hamaidi, M. Meloxicam-Paracetamol Binary Solid Dispersion Systems with Enhanced Solubility and Dissolution Rate:Preparation, Characterization and In Vivo Evaluation. J. Pharm. Innov. 2017, 12, 206–215.

51. Li, W.; Qing, S.; Zhi, W.; Yao, H.; Fu, C.; Niu, X. The pharmacokinetics and anti-inflammatory effects of chelerythrine solid dispersions in vivo. J. Drug Deliv. Sci. Technol. 2017, 40, 51–58.
52. Onoue, S.; Nakamura, T.; Uchida, A.; Ogawa, K.; Yuminoki, K.; Hashimoto, N.; Hiza, A.; Tsukaguchi, Y.; Asakawa, T.; Kan, T.; et al. Physicochemical and biopharmaceutical characterization of amorphous solid dispersion of nobiletin, a citrus polymethoxylated flavone, with improved hepatoprotective effects. Eur. J. Pharm. Sci. 2013, 49, 453–460.
53. Balata, G.; Shamrool, H. Spherical agglomeration versus solid dispersion as different trials to optimize dissolution and bioactivity of silymarin. J. Drug Deliv. Sci. Technol. 2014, 24, 478–485.
54. Hwang, D.H.; Kim, Y.-I.; Cho, K.H.; Poudel, B.K.; Choi, J.Y.; Kim, D.-W.; Shin, Y.-J.; Bae, O.-N.; Yousaf, A.M.; Yong, C.S.; et al. A novel solid dispersion system for natural product-loaded medicine: Silymarin-loaded solid dispersion with enhanced oral bioavailability and hepatoprotective activity. J. Microencapsul. 2014, 31, 619–626.
55. Zawar, L.R.; Bari, S.B. Preparation, characterization and in vivo evaluation of antihyperglycemic activity of microwave generated repaglinide solid dispersion. Chem. Pharm. Bull. 2012, 60, 482–487.
56. Pokharkar, V.; Kutwal, M.; Mandpe, L. Pioglitazone Solid Dispersion System Prepared by Spray Drying Method: In Vitro and In Vivo Evaluation. PDA J. Pharm. Sci. Technol. 2013, 67, 23–34.
57. Moreira, C.D.L.D.F.A.; Pinheiro, J.G.D.O.; Da Silva-Júnior, W.F.; Barbosa, E.G.; Lavra, Z.M.M.; Pereira, E.W.M.; Resende, M.M.; De Azevedo, E.P.; Quintans-Júnior, L.J.; Araújo, A.A.D.S.; et al. Amorphous solid dispersions of hecogenin acetate using different polymers for enhancement of solubility and improvement of anti-hyperalgesic effect in neuropathic pain model in mice. Biomed. Pharmacother. 2018, 97, 870–879.