

Therapeutic Applications of Solid Dispersions

Subjects: Pharmacology & Pharmacy

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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.

Keywords: 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 ^[6], 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.

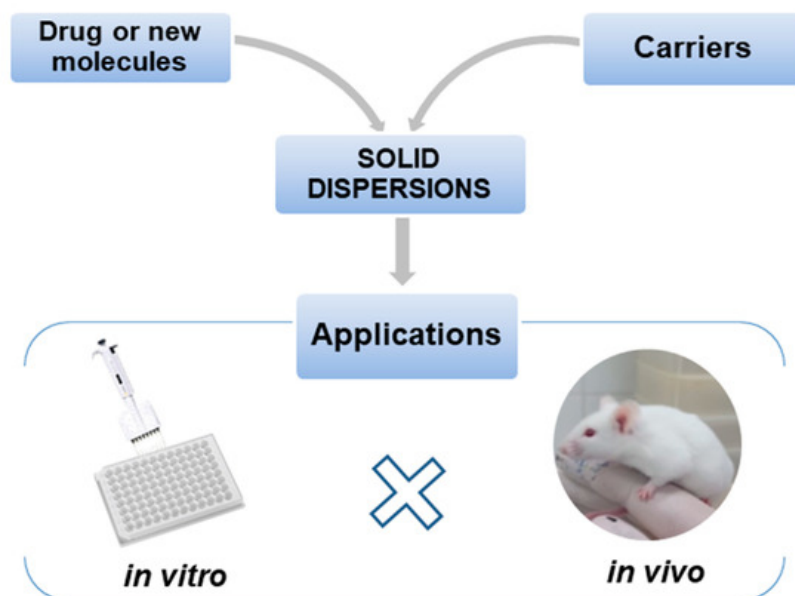


Figure 1. Representation of the application of solid dispersions in biological assays.

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](#).

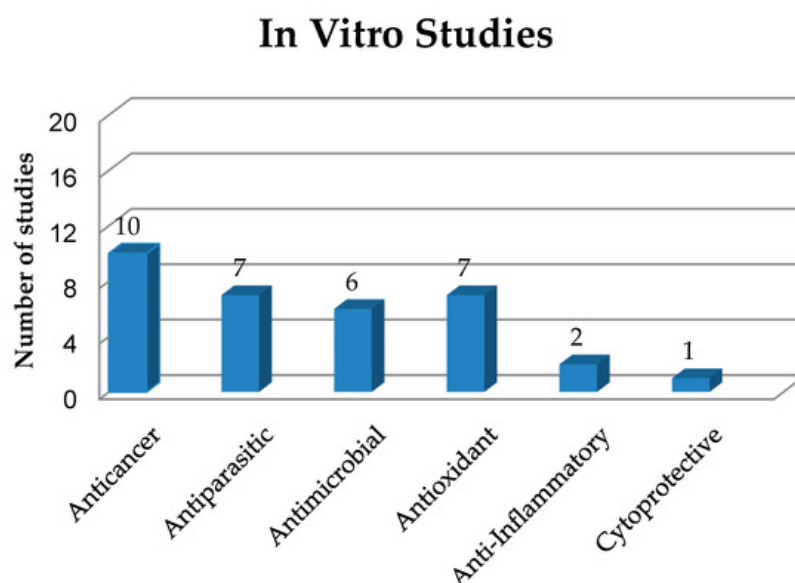


Figure 2. Quantification and classification of *in vitro* studies on solid dispersions published in the period from 2009 to 2020.

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 IC ₅₀) than the niclosamide solution.	[11]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
OHPP	Paclitaxel	PC-3, HeLa, A549	Anticancer	SDs showed significantly higher cytotoxicity to target cells (lower IC50) than the paclitaxel solution.	[12]
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]
		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.	
Poloxamer 407	Curcumin (CM)	AChE, BChE, GST, MAO A-B	Enzyme inhibitory /Antioxidant	SD was able to inhibit the activities of AChE, BChE and GST in aqueous medium.	[15]
		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]
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 <i>Trypanosoma cruzi</i>	Antichagasic	SDs enhanced drug solubility, release kinetics and parasitic activity.	[21]
Low-substituted HPC	Benznidazole	Epimastigotes and intracellular amastigotes of <i>T. cruzi</i> (CL-B5)	Antichagasic	SDs had higher antiparasitic activity against amastigotes than epimastigotes.	[22]
Gelucire 50/13	Ursolic acid	Trypomastigotes of <i>T. cruzi</i> Y	Antichagasic	Increased antiparasitic activity.	[23]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
PVP K30,PVP/VA, Kollidon-CL-M, sodium starch glycolate	Praziquantel	Adult schistosomes of <i>Schistosoma mansoni</i>	Antischistosomal	Increased solubility, better bioavailability and stronger antiparasitic activity.	[24]
PVP K30	Praziquantel	Newly transformed schistosomula of <i>S. mansoni</i> 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 <i>Plasmodium falciparum</i> 3D7	Antimalarial	Increased dissolution rate, amorphous form, increased solubility and, mainly, increased antimalarial activity.	[26]
Soluplus, Kollidon VA64, Plasdane S630	Lumefantrine	ITG cells	Antimalarial	Increased antiparasitic activity.	[27]
Chitosan	Abietic acid	<i>Staphylococcus epidermidis</i>	Antimicrobial	SD exhibited better MIC values against <i>S. epidermidis</i> than chitosan and abietic acid alone.	[28]
		DPPH radical scavenging	Antioxidant	SD had higher antioxidant power (IC ₅₀ of 0.61 mg/mL) than abietic acid alone (IC ₅₀ of 11 mg/mL).	
PVP K30 and HPMCAS	Griseofulvin	Dermatophytes of <i>Trichophyton rubrum</i> NCPF 935	Antimicrobial	SDs significantly reduced biofilm formation when compared to the control.	[29]
Pluronic F127	Gatifloxacin	<i>Staphylococcus aureus</i>	Antimicrobial	The gatifloxacin/Pluronic F127 system exhibited antimicrobial efficacy when compared to commercialized eye drops.	[30]
PVP K30	Curcumin	<i>Salmonella enteritidis</i>	Antimicrobial	SD had a strong antimicrobial effect on <i>S. enteritidis</i> , while CM alone did not show antimicrobial activity <i>in vitro</i>	[31]
HPMC	Curcumin	<i>Escherichia coli</i>	Antimicrobial	SD used to prepare phototoxic supersaturated solutions showed significant bactericidal activity against <i>E. coli</i> .	[32]
Polaxamer 407	Curcumin	<i>E. coli</i> , <i>Pseudomonas aeruginosa</i> and <i>S. aureus</i>	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 ± 0.03 ≤ IC ₅₀ ≤ 1.00 ± 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 <i>in vitro</i> .	[35]

Carrier Type	Substance	Cell Type	Activity	Improved Characteristics	Reference
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 phytylglycogen; IC₅₀, Half inhibitory concentration; PVP/VA, Polyvinylpyrrolidone/vinyl acetate; TPGS, D- α -toco-phenyl 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](#).

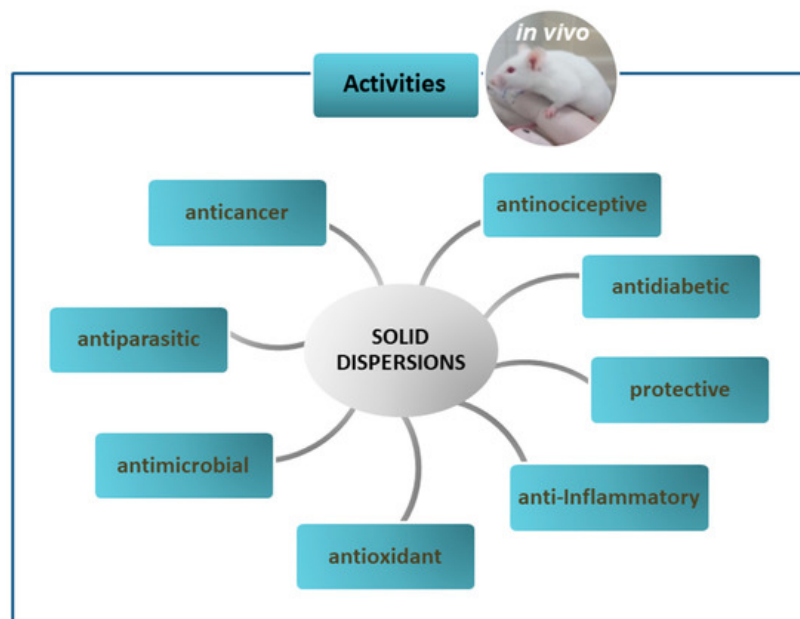


Figure 3. *In vivo* activities of solid dispersions.

In Vivo Studies

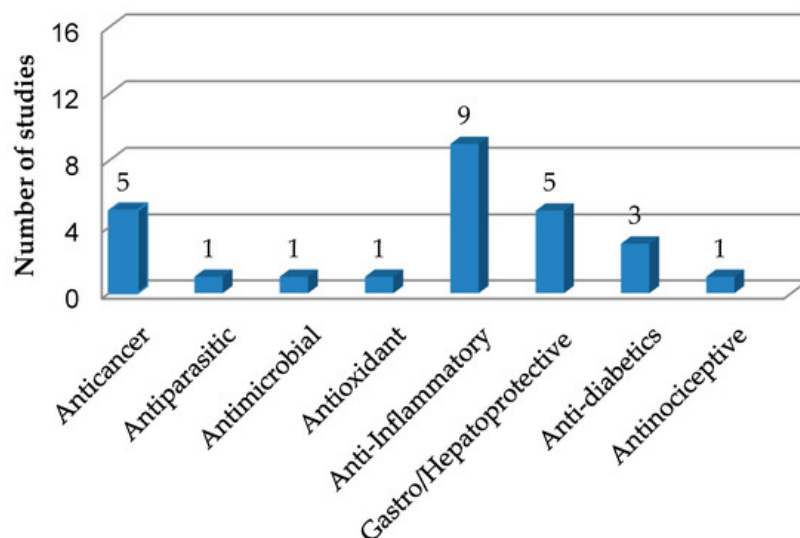


Figure 4. Quantification and classification of *in vivo* studies on solid dispersions published in the period from 2009 to 2020.

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]
(+)-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	<i>Selaginella doederleinii</i> 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]

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
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 <i>Salmonella enteritidis</i> 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 glutathione level.	[42]
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-1 β 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/cm ² (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 inhibition after 6 h.	[48]
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]

Carrier Type	Substance	Animal	Dose	Activity	Improved Characteristics	References
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]
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]

PVP, Polyvinylpyrrolidone; SD, Solid dispersion; HPC, Hydroxypropyl cellulose; CM, Curcumin; CM/PVP SD, curcumin/polyvinylpyrrolidone solid dispersion; SOD, Superoxide dismutase; PEG, Polyethylene glycol; TNF- α , tumor necrosis factor alpha; IL, interleukin; NO, Nitric oxide; HPMC, Hydroxypropyl methylcellulose; AST, Aspartate aminotransferase.

4. Conclusions

Solid dispersions are a technological strategy to improve the pharmacological potential of natural or synthetic bioactive molecules, thanks to an increase in their solubility and bioavailability, thus leading to possible enhancement of their biological activities. In this context, this review sought to summarize and critically examine studies conducted with this approach both *in vitro* and *in vivo*, which have provided evidence of a significant therapeutic potential that solid dispersions could offer in the context of the most diverse biological activities.

As poorly water-soluble active ingredients incorporated in solid dispersions exhibited improved physicochemical and pharmacological properties, these systems can be targeted in the pharmaceutical industry as possible therapeutic alternatives for certain diseases, with greater selectivity, safety and efficacy than the existing treatments.

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