Multicomponent solid dispersion a new generation of solid dispersion produced by Spray-Drying

Laura Modica De Mohac[a], Bahijja Raimi-Abraham[b], Roberto Caruana[c], Giammona Gaetano[d], Mariano Licciardi[d*]

[a]Dipartimento Promozione della Salute, Materno-Infantile, di Medicina Interna e Specialistica di Eccellenza "G. D'Alessandro" (PROMISE), Palermo, Italy.

[b]King's College London, School of Cancer and Pharmaceutical Sciences Institute of Pharmaceutical Science Faculty of Life Sciences and Medicine, Franklin-Wilkins Building, 150 Stamford Street, London SE1 9NH, UK.

[c]Advanced Technologies Network Center (ATeN Center), University of Palermo - Viale Delle Scienze – Edificio 18 – 90128, Palermo, Italy

[d]Dipartimento di Scienze e Tecnologie Biologiche Chimiche e Farmaceutiche (STEBICEF), Università di Palermo, Via Archirafi, 32, 90123, Italy.

Abstract

The term "multicomponent solid dispersion" is widely used in recent literature to describe solid formulations consisting of a special excipient's mixture and active molecules finely dispersed. However, this term has not yet been defined. In this review, we aimed to improve the definition of multicomponent solid dispersions as a new generation of solid dispersions capable to improve both formulation issues and the therapeutic effect of the final dosage form. As it is well-known the use of solid dispersions to improve drug dissolution rate and solubility, this review describes the field of solid dispersions as well as the formulation strategies available for their production. In particular, the review highlights the use of the spray-drying technique and the benefits provided by this method in the manufacturing of multicomponent solid dispersion.

Keywords: multicomponent solid dispersion, spray-drying, dissolution rates, dosage form, polymers.

1. Introduction

The term “solid dispersion” describes a solid product containing at least two different components, generally a hydrophilic matrix and a hydrophobic drug[1]. It was, at first, used to describe a eutectic compound where the drug is present in a microcrystalline state by Sekiguchi and Obi[2]. Later, Goldberg and co-workers[3] described it as a system where the drug is dispersed in a suitable polymer with high aqueous solubility and once the solid dispersion is exposed to an aqueous media the hydrophilic carrier dissolves, releasing the drug as very fine particles. Most recently, a solid dispersion was described as a delivery system whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability[4,5]. According to Noyes and Whitney equation and Nernst-Brunner theory, the dissolution rate is directly proportional to the surface area of the drug and its increase by the decreasing of the particle size achieves enhancement of the dissolution rate[3]. The use of solid dispersion in the industry became mandatory to overcome the most common problem faced in drug delivery: drug solubility. Solubility is the property of a solid to dissolve in a liquid solvent to form a homogeneous solution of the solute in the solvent. Usually, drugs are classified according to their solubility and permeability through cellular membranes is the Biopharmaceutical Classification Systems (BCS) and thus organized in four classes, from I to IV. The 40 % of the New Chemical Entity (NCE) is hosted into the II (drugs with low solubility and high permeability) and IV (drugs with low solubility and permeability) classes for oral administration, due to their high hydrophobicity[6,7]. Drugs with low solubility represent a significant challenge in the drug-delivery formulation and several pre-formulation strategies were employed in order to overcome this issue such as salt formation[8], micronisation[9], nano-fiber formation trough electro-spinning or microfluidics and most commonly solid dispersion[10–13]. Solid dispersions represent the most common and useful pharmaceutical strategy applied to increase

the dissolution, absorption, and therapeutic efficacy of drugs in dosage forms. Their wide use in the pharmaceutical field is due to the high number of advantages that solid dispersions offer, in particular, if they are produced in the form of particles with very small dimensions, which therefore increase the specific surface of the solid and consequently a greater dissolution rate[14]. Furthermore, if special excipients are used in the solid dispersion, able to improve the wettability of the particles, an additional positive result is obtained due to the improvement of wettability, i.e. an increase of solubility and therefore of bioavailability[15]. The suitability of solid dispersion in pharmaceutical industry manufacturing is proved through the years by approbation by the Food and Drug Administration agency of many products available on the market[16]. Another aspect that needs to be considered in drug delivery formulation is the morphological states of the drug. As it is well-known, product in the solid-state could be either crystalline or amorphous which differ for the energetical state of the molecules packed with the solid. Compound with a short-range molecular order and high kinetic energy, like the amorphous solid, results to have easily broken bonds, therefore they are more soluble and have faster dissolution rate. Within the solid dispersion, the drugs are usually incorporated as supersaturated solutions, that is a physical condition very similar to the amorphous form, thus justifying the increase in the drug solubility[17].

Solid dispersion could be produced by a large range of techniques such as solvent casting method[10], freeze-drying[18], hot-melt extrusion[19], electrospinning[20], wet-milling[21] and spray-drying[22]. In this review we aimed to analyse the advantage in the use of spray-drying to formulate novel multicomponent solid dispersion, giving a definition of and an overview on its use of, to produce, at first, solid dispersion and, then, multicomponent solid dispersion for application in the field of pharmaceutics.

2. Spray-drying

Spray-drying is a formulation technique where a mixture of excipients, commonly a polymers dispersion, containing a drug, is atomized, sprayed and dried in a chamber by a heated gas stream

(generally air)[23]. This technique offers several advantages as it is suitable for thermolabile compounds because the heat inlet gas gets in touch with the inlet sample, which possesses high humidity, allowing rapid solvent evaporation and, consequently, cooling down of the chamber temperature. Through spray-drying is possible to influence the final product characteristic calibrating the different parameters such as inlet and outlet temperatures, pump velocity and aspiration percentage and solvent selection, as recently Reviewed by Paudel et al. (in 2013)[24] and Singh and Van den Mooter (in 2016)[25]. Parameters' effects on spray-dried particles are summarized in table1.

Table 1. Spray-drying parameters effects on particles

Temperature effects	Higher inlet temperatures and a low difference between inlet and outlet temperatures allow obtaining dried particles. The increase of this difference might affect particle water content with high humidity resulting[25].
Pump and Aspiration	Increase in pump velocity decreases outlet temperature this enhance the difference between inlet and outlet temperature so increase the humidity of the product. Low aspiration reduced the particle water content[26].
Solvents	Solvents with a low boiling point are easy to evaporate and allow to obtain dried particles[23].

Spray-drying technique has several applications in the pharmaceutical and food industries. In this latter, it is exploited to create new functional food such as nano-functional foods[27], encapsulation of fruit aromas and fish oil[28], essential oils and perfumes[29]. In the last two decades, researchers studied the use of spray-drying to obtain pharmaceutical products and formulate a drug delivery

system as solid dispersion for inhalation[30], stabilize insulin[30] and thermolabile vaccine[31], incorporate additives for drug control release[32].

2.1 *The role of polymers in solid dispersion manufacturing via spray-drying*

Spray-dried solid dispersions were widely studied in the last decades as an option to improve dissolution rate and in turn bioavailability of poorly water-soluble drugs such as the one classified as BCS class II and IV. This technique is useful to obtain spherical particles whit small size and narrow distribution. Those characteristics are not only due to the spray-drying technique itself but are also affected by polymers ratios and properties. Usually, the appropriate polymers are selected after pre-formulation studies, in which potential effects are evaluated such as the ability to increase the dissolution rate of the drug, stabilizer or dispersing agent for the formulation itself. Therefore is needed to consider parameters such as glass transition, presence of chemical groups which might link the drugs during formulation, hygroscopicity, solubility in the selected solvent, and thermal stability[33].

As above mentioned, solid dispersion is an easy methodology that allows obtaining stable products. However, pharmaceutical technologists have the challenge to optimise drug delivery systems through the chosen of the right combination of polymers ratio and concentration for the desired formulation. To overcome this issue, polyvinylpyrrolidone (PVP) was used from several authors due to its properties, such as tackiness, film-formation, dispersant, and thickener, in order to produce tablets, sugar and film coating, and in the formulation of many drug delivery systems.[34] In spray-drying formulation, it is common to use high molecular weight PVP, best known as Kollidon®, as it has a high glass transition, about 178°C, and thus is suitable for many temperatures used with spray-drying[35]. The literature presents many pieces of evidence while using PVP for solid dispersion manufacturing via spray-drying; Wlodarski and co-workers carried out a pre-formulation study in which were shown the solubilising effect of PVP despite other polymers, able to the increase of twenty times the pure drug solubility[36]. In 2016, Haser and co-workers

evaluated PVP effects on drug morphological stability. The study showed PVP suitability in maintaining the drug in the correct morphology conformation avoiding Naproxen modification which would affect formulation stability[37]. In addition to PVP used to confer improved solubility and stability to solid dispersion particles, in the last years a novel polymer, named Soluplus® (SLP) was introduced to the market due to its influence on enhancement of drug bioavailability and dissolution rate of low aqueous solubility API[38–40]. SLP is a novel polyvinyl caprolactam-polyvinyl acetate-polyethylene glycol graft copolymer with amphiphilic structure[38]. Since 2012 SLP revealed to be suitable to solid dispersion production through spray-drying by using "soft" inlet temperature conditions, due to its glass transition temperature of about 70°C. As SLP is a water-soluble polymer, its addition in solid dispersion formulation always led to a solubility enhancement of the API's solid dispersion. In 2012 Shamma and co-workers reported the use of SLP to formulate solid dispersion of carvedilol, increasing its dissolution rate[41]. Most recently, in 2017, many authors used this polymer to reach the goal of increased drug bioavailability and solubility, such as nifedipine and sulfamethoxazole[42], indomethacin[43], and itraconazole[44].

Another polymer currently employed in solid dispersion manufacturing is PEG6000[45,46]. Usually, solid dispersion with high PEG6000 concentration gave the best dissolution profile compared to the other polymers as showed by Homayouni and co-workers in a celecoxib oral formulations[47]. Later, in 2017, Lu and co-workers prepared solid dispersion of azilsartan with PEG6000 via spray-drying and compared the dissolution profile of the formulation with tablet available on the market, Azilva®. Authors demonstrated that thanks to the polymer the formulation has a comparable dissolution profile (to Azilva) and that maintains the drug crystallinity during formulation and shelf life[48].

It is noteworthy that the spray-drying technique also allows the designing of a particle with reduced size as low as much needed for many disease treatments different from oral administration, such as pulmonary and ocular delivery. Those administration routes imply different absorption and different drug bioavailability so it due to using adequate polymers. In the last years, particles made from

biodegradable poly d,l-lactic-*co*-glycolic acid (PLGA) were explored as delivery vehicles for therapeutics due to their biodegradability that could protect macromolecules from instant degradation *in-vivo* while allowing tenable release rate and profile[49]. In 2017 Anzar and co-workers prepared a submicron particle of simvastatin-loaded PLGA via spray-drying. In this study, Simvastatin is proposed as an anti-cancer active due to its capacity to inhibit cell proliferation. The particles were formulated to be administrated by the pulmonary route. The submicronic particles obtained through the spray-drying formulated by this method was found suitable in terms of its morphological characters, encapsulation efficiency, loading capacity, cytotoxicity studies, and pharmacokinetic parameters[50]. PLGA suitability in microparticle formation was also shown from Takeuchi and co-workers, describing the production of rifampicin-PLGA solid dispersion. The use of PLGA demonstrated that a higher concentration of the polymer induced a higher microparticles phagocytotic ratio of alveolar macrophages[51]. Another biocompatible polymer investigated for spray-drying solid dispersion manufacturing is the polysaccharide inulin. It has several applications in food and pharmaceutics; due to its chemical structure containing β-1,2 linkages, the polymer is not hydrolysable by human digestive enzymes[52,53]. However, due to the capacity of intestinal microbiota to degrade the β-1,2 bonds, inulin is used as prebiotic and as colon targeting in a controlled drug delivery system[53].

A wide literature demonstrated how polymers selection affects the final formulation characteristics, in terms of stability, dissolution rate, and external aspect. Moreover, a wise selection of polymers could reduce dosage forms side effect and target the drug distribution.

3. Multicomponent Solid dispersion (MSD)

The term multicomponent solid dispersion was introduced in 1987 by Shadrina and co-workers, but since then it was defined till 2006 the year in which Yoo and co-workers and Pongpeerapat introduced the definition of “ternary solid dispersion”, prepared with more than two polymers in the carrier matrix[52, 53]. Then, in 2013, Singh and Van den Mooter described the MSD as a system in

which the addition of a third or even fourth component would improve the performance of the solid dispersions[25]. But, it is just in 2016 that Haneef and Chadha described the therapeutic advantage in formulation of multicomponent solid dispersion as a drug-drug cocrystals solid compacted in a supramolecular complexes comprising two or more therapeutically effective components that represent a reliable method to improve physicochemical properties of drug delivery systems in order to achieve therapeutic advantages[55, 56]. However, this definition includes just formulation in which both drugs and polymers are in the crystalline state, conditions that are low represented in the most common drug delivery systems, in which amorphous polymers and drugs are used. Moreover, with such a definition, the achievement of a therapeutic advantage is related to the formation of a physical complex between two drugs, but no scientific evidence demonstrated the effect of the polymers in enhancing the system potential.

In this review we defined the term multicomponent solid dispersion as a solid system in which one or more drugs are dispersed in a carrier matrix composed by at least two compounds whose possess properties capable to modify or enhance the drug delivery system in term of improving drug release, improving drug permeability through membrane or increase system adhesivity to the mucosa. Those represent an evolution of the usual solid dispersion that has as the main aim the increasing of the drug release profile.

Multicomponent solid dispersion offers as further advantage their use in multi-drug therapy because it can be produced containing more than one active pharmaceutical, allowing the therapeutic dose to be properly delivered by the selection of the right polymer's combination. The nature of the compounds with which the multi-component solid dispersion is made may affect the thermodynamic stability of the solid, resulting in morphological modification of the final product and thus affecting the drug bioavailability[58–60]. Another advantage is related to the possibility of selecting different manufacturing strategies employable to produce multi-component solid dispersions, as being the same as the one used to produce solid dispersions.

In literature, the general examples of solid dispersions were classified into four different generations according to drug and carrier morphology. It is the author's opinion that a fifth generation should be included, and this should comprehend the multicomponent solid dispersion. In table 2 is summarised the newest and most updated classification of solid dispersion generation. That includes the definition of the new fifth generation. In the next subchapter, this generation was investigated according to literature findings.

Table 2. New proposed classification of solid dispersions.

Generation	**Composition**
First	Eutectic in which both drug and carrier are in the crystalline state[57].
Second	Both drugs and carriers in the amorphous state with the drug supersaturated in the molten matrix [61].
Third	System of multiple carriers that present self-emulsifying properties which let to improve drug solubility and system stability[62].
Fourth	Solid dispersion prepared by the use of the amphiphilic chemical structure of SLP[41].
Fifth	A solid system in which one or more drugs are dispersed in a carrier matrix composed by at least two compounds whose possess properties capable to modify or enhance the drug delivery system in term of improving drug release, improving drug permeability through membrane or increase system adhesivity to the mucosa.

3.1 *Fifth Generation: Formulation of multicomponent solid dispersion*

The literature presented many examples of the different pharmaceutical techniques used to prepare this novel generation of solid dispersion. In previous work, Eddleston and co-workers, highlight the advantage the freeze-drying to avoid problems caused by differences in the solubilities, used to prepare cocrystal containing two or more pharmaceutical compounds, with the final aim to create a novel mixture of caffeine and theophylline[63]. Such formulation, if brought to the market, could bring to combination therapy of the two molecules in the treatment of bronchoconstriction. The solvent evaporation method was used quite often in order to prepare multicomponent solid dispersion of different poorly water-soluble drugs such as gliclazide and tromethamine with the final funding of the promotion of the dissolution behaviour and absorption of both drugs, due to an improved drug wettability and hydrophilicity[64]. Enhancement in both solubility and bioavailability was found as well by Chadha and co-workers, who prepared multicomponent solid dispersion of felodipine to improve the treatment of hypertension. In particular, *in-vivo* studies showed a decrease in systolic blood pressure compare with a pure drug not formulated[57]. Finally, the wet-willing method was used to stabilised and improved the bioavailability of a multi-component system of the antitumor bufadienolides in combination with croscarmellose sodium and sodium lauryl sulfate.

In the next chapter, the review focuses on the production of multicomponent solid dispersion via spray-drying and on the advantages offered by this method.

3.1.1 Manufacturing of multicomponent solid dispersion via spray-drying

As stated before, by multicomponent solid dispersion is it possible to achieve both formulating and therapeutic goals. Such an advantage was used by Punčochová and co-workers, to overcome both formulation stability and poor water solubility of the antiemetic aprepitant. Researchers formulated a multicomponent solid dispersion system by the use of two polymers, polyvinylpyrrolidone (PVP) and Soluplus® (SLP), which addiction allowed the manufacturing of a delivery system as microparticles with increased release and thermal stability[65]. In particular, the higher release

compared to the pure drug was due to a dry core composed of the drug entrapped in an external coating that formed a gel layer of increasing thickness during dissolution. The formation of a dry core-shell is usual in the spray-drying process due to the different temperature at which the sample is exposed first into the atomizer and later in the heating chamber[66,67]. Another example was provided by Jug and co-workers, who produced multicomponent solid dispersion of piroxicam and cyclodextrins and hydroxypropyl methylcellulose (HPMC) to improve the stability of the system as well as increase the complexation efficiency. Those results in an increase of drug permeability through the membrane investigated by Franz diffusion cell[68]. Such an increase in drug solubility was attributed to the reduced particle size and improved wettability of the particles. Moreover, the spray-drying reduced the drug into the amorphous state causing an increase of the dissolution rate. The effect of spray-drying of wettability and particle size is well-known and coherent with many literature findings[26,69].

One of the most successful examples of the use of the spray-drying in the production of multicomponent solid dispersion was given by Shefer in 2003. In this work, a controlled release system of biologically active ingredients or sensory markers incorporated into solid nano-particles was produced to permeate the oral cavity mucosae and mucous membranes of various tissues[70]. To achieve this result a selection of different polymers were used, such as poly(acrylic)- and/or poly(methacrylic) acid (e.g., Carbopol, Carbomer), poly(methylvinyl ether/maleic anhydride) copolymer, and their mixtures and copolymers, carboxymethylcellulose (CMC) and hydroxypropylmethylcellulose (HPMC).

It is well-known that spray-drying appeals due to its simplicity and adaptability to a different compound. In 2013, it was used by a research group at Monash University, to prepare dried powder suitable for pulmonary delivery of bio-macromolecules within a sugar-based carrier[71]. Thanks to the spray-drying it is possible to prepare solid spheres with a diameter lower than 5μm, required for such administration route[72]. Such studies showed the suitability of spray-drying to the use of different compounds as biomolecules or sugars.

In 2018, Baghel and co-workers prepared a dosage form of dipyridamole and cinnarizine using different surfactants such as sodium dodecyl sulfate and poloxamer 188 and HPMC. The spray-dried multicomponent solid dispersions were able to maintain a higher supersaturation condition that allowed rapid dissolution behaviour and higher system stability over shelf-life[56]. Most recently, in 2019, Modica de Mohac and co-workers, successfully prepared a multicomponent solid dispersion of the anticancer irinotecan to improve its formulation orally by increasing its permeability through the intestinal mucosa. To achieve this aim, the carrier inulin was used to both increase the permeability and to potentially protect the intestine from diarrhea, the most common side effect of the drug. Moreover, the polymer cellulose acetate phthalate was added to the formulation to protect the drug from the gastric environment, achieving the formulation of a controlled-release dosage form[73].

3.1.2 The advantage of using the spray-drying in the formulation of multicomponent solid dispersion

The use of spray-drying to produce multi-component solid dispersion presents several advantages. As it is just a single step manufacturing it possesses the capacity to incorporate, at the molecular level, multiple components (i.e. drugs, polymers, excipients) into a particle. The particle characteristics could be easily modified in terms of dimension, wettability, and density by modifying different parameters of the production process, as described in Table 1. Moreover, the spray dryer systems are suitable for different kinds of liquid dispersions such as solution, suspension, emulsion and colloids[74–77]. The spray-drying process is, as well, suitable for thermolabile products, either drugs or excipients, by optimizing the inlet and outlet temperatures. In particular, by modifying the inlet temperatures although outlet was found to affect several physical properties such as solubility and to decrease in bulk density, moisture content, and water activity.[78] The results are the manufacturing of a solid product with suitable particle size (to the targeted administration route), good dispersibility and solid-state properties. Spray-drying gives also

the great advantage to obtain particle completely dried. In order to prepare stable dosage forms as a solid dispersion, the process needs to be carried with suitable solvents (organic or not) that totally evaporate allowing the formation of dried powders. The preferred solvent used for spray-drying is water. In terms of multicomponent solid dispersion for oral administration, the use of water as a vehicle of feed dispersion allows testing polymer-drug mixture in a condition like the physiological environment. Moreover, water allows us to obtain totally dried particles, is biocompatible, easy to obtain and economic. The use of this solvent could be an advantage for the industry that could avoid cost for apparatus usually needed while using organic solvent via spray-drying also to remove organic impurities[79,80].

4. Conclusion

In this review multicomponent solid dispersion was defined as the fifth generation of solid dispersion where the combination of two or more compounds both improves the dosage form manufacturing process (such as drug stability and shelf-life) as well as increases its therapeutic performance (i.e. improve permeability, reduce side effect, increase bioavailability). Spray-drying was suggested as the most suitable method in order to produce such a system as it provides flexibility in the selection of solvents, range of temperatures, kind of liquid dispersions injectable and pump speeds. The changing of these parameters was proved to modify the final product properties improving particle size homogeneity, wettability, moisture content, and solubility, through the reduction of the particle size. Finally, the combination of the technological advantage offered by the spray-drying combined with the formulation benefits provided by the selection of suitable compounds within multicomponent solid dispersion would lead to the manufacturing of a most complete and functional drug delivery system.

The reported literatures showed how wide is the formulation of solid dispersion in drug delivery. Such formulations cover mostly all the drug dosage forms available today in the market. However, researchers are still working to improve such system in order to reduce the side effects related to

polymer's toxicity or effect on drug metabolism. It is the author's opinion that the preparation of smart formulations should be preferred. Those, would ideally just contain a polymer mixture, consisting of just a few polymers, with both formative and therapeutic effects. If for example, it is required to prepare microparticle via spray-drying, it would be appropriate to use a polymer able to encapsulate the maximum amount of drug, protect the drug stability improving the shelf-life. Ideally the polymers selection would as well improve drug bioavailability and permeation through the membrane.

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