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Solid dispersions: An evergreen solubility enhancement technique for hydrophobic drugs

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ABSTRACT

Oral route is the most preferable route of drug delivery for most of the drug but it is not suitable for the drugs which are poorly water soluble. It mainly affects the oral bioavailability of the drugs. It remains as a most challenging aspect in formulation development due to its minimal solubility. To overcome this problem formulation scientists have employed the different techniques. One of the techniques is solid dispersions. These are gaining attracted considerable interest as an efficient means of improving the solubility and dissolution which results in increasing the bioavailability of poorly water soluble drugs. The present article mainly focus on the areas of basic concept of solid dispersions, advantages, disadvantages, types and various methods of preparation for solid dispersions.

Key words: Solid dispersions, hot melt extrusion method, solvent evaporation, fusion method, etc.

INTRODUCTION

The therapeutic activity of an active moiety of the formulation is seen when it is in solution or in solubilized form in the systemic circulation. But this can be observed in case of drugs which are having high solubility but not in drugs which are having poor aqueous solubility. This presents a major challenge for the formulation scientist to enhance the solubility of poorly water soluble drugs as the solubility parameter is directly related to the bioavailability of the drug. Because the drugs which are administered through oral route should solubilized in the gastrointestinal fluids before the absorption into systemic circulation.

The interrelationship between the rate of dissolution and absorption was given by Noyes Whitney equation as the rate of dissolution is directly related to the solubility of the drug molecules and the equation was given as follows[1]

$$\frac{dc}{dt} = \frac{DA}{h}(C_S - C) \qquad \text{Eq. 1}$$

Where dc/dt = rate of drug dissolution at time't'
D = Dissolution rate constant
A = Surface area of the particle
Cs= maximum drug solubility
C = concentration of the drug in the bulk of the solution
h = thickness of the stagnant layer

Most of the new chemical entities (NCE's) which are developed or in developing stage fails the phase studies due to their limited solubility and permeation in the biological matrix. These limitations can be overcome by employing the techniques to improve the solubility and permeability which helps in reduction of toxic or adverse effects when they are administered in high doses to produce the pharmacological action and also improves the safety and efficacy of drugs.

The solubility of the drug molecules can be enhanced by employing the techniques which mainly act by imparting or inducing the modifications in their physicochemical properties of the drug substance [2]. Various methods which includes reduction in particle size (micronization, nanonization), complexation (inclusion complexes by using cyclodextrins), solid state modification (polymorphs, pseudopolymorphs), salt formation, prodrugs and by alteration of pH in the drug microenvironment[3]. The permeation of drug was mainly enhanced by employing various techniques like applying lipid technologies or by incorporating the permeation enhancers or improvers in the formulation or by ion pairing approach.

One of the strategies where most of the researchers focus on the enhancement of the solubility is solid dispersions. The term "solid dispersions" was first time used by sekiguchi and obi in 1961 by using eutectic mixtures for the solubility enhancement [4]. According to Chiou and Riegelmann the term "solid dispersion" was defined as "dispersion involving the formation of eutectic mixtures of drugs with water soluble carriers by melting of their physical mixtures" [5]. The final product which is formed by transformation of a fluid-drug carrier combination into solid amorphous form. The main purpose of formulating solid dispersions is to improve the dissolution rate of poorly soluble drugs. Some of the examples of drugs which are having poor water solubility whose solubility is enhanced by solid dispersions are piroxicam [6], carvedilol [7], roixthromycin [8], efavirenz [9] and aceclofenac [10].

The dissolution equation is given by [11]

$$\frac{dm}{dt} = -K.A\,(S - C) \qquad \text{Eq. 2}$$

Where m = amount not dissolved
K = intrinsic dissolution rate constant
A = surface area
S = solubility
C = concentration at't' time

The arena of solid dispersions is increasing day by day in the field of pharmaceutical industries because of their advantages over than the other techniques used for enhancement of solubility.

COMPONENTS OF SOLID DISPERSIONS [12]:

The main components of the solid dispersions are:

1. Hydrophobic drug
2. Hydrophilic matrix

Hydrophobic drug is the active ingredient which has limited solubility in the aqueous phase and the hydrophilic matrix mainly consists of carrier which plays prominent role in enhancing the solubility of the hydrophobic drug.

Ideal Requirements of Carriers [13]:

The ideal characteristics of carrier which are used in solid dispersions are

- It should be non toxic and inert in nature
- It should shows good water solubility (improves wettability and dissolution)
- The glass transition temperature (T_g) of the carrier should be high. (To produce amorphous structure).
- The melting point of the carrier should be low. (Stable formulations were obtained.)
- The solubility profile of the carrier should be similar with the profile of drug.

Classification of solid dispersions based on carriers [14]:

The carriers of solid dispersions are mainly classified as

1. First generation
2. Second generation

3. Third generation

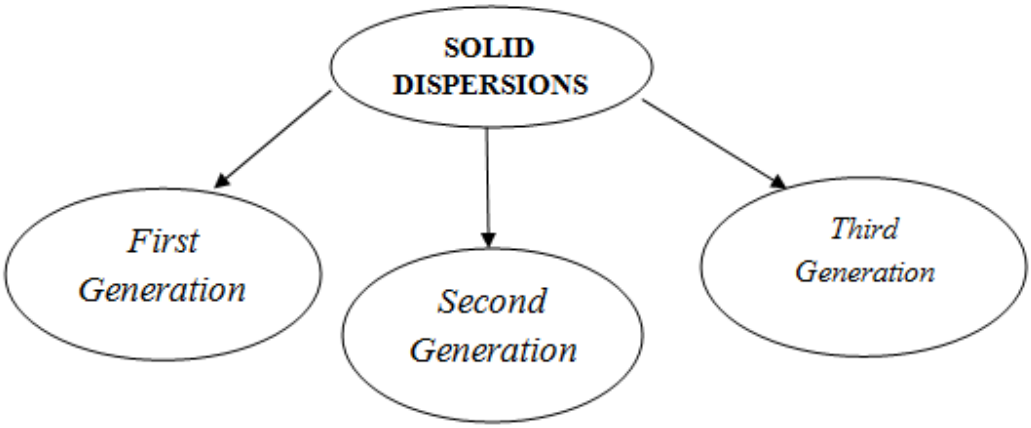

Figure 1: Classification of Solid Dispersions Based on Nature of Carriers

First generation:
In these systems, both the carrier and drug are in crystalline state.
Ex: Eutectic mixtures

Second generation:
The carriers which are used in these systems are in amorphous state while the drug is in either crystalline or amorphous form. Polymeric substances are used as carrier.

Third generation:
Surfactants and polymeric substances or combination of these two substances are used as carriers in the formulation of solid dispersions.

Table 1: Examples of carriers of solid dispersions

Solid Dispersions	***Categories of Substances***	***Examples***
First generation	Eutectic Mixtures	Urea, Sugars, Organic Acids
Second generation	Polymeric Substances	Polyethyleneglycols(PEGs), Polymethacrylates, Hydroxy Propyl Methyl Cellulose, Cyclodextrins
Third generation	Surfactants	Poloxamer 408, Gelucire 44/14, Tween 80

TYPES OF SOLID DISPERSIONS [15],[16]:
The various types of solid dispersions are categorized into the following ways:
1. Simple eutectic mixtures
2. Amorphous precipitation in crystalline matrix
3. Solid solutions
4. Glass solution and glass suspensions
5. Other categories

Simple eutectic mixtures: Eutectic mixtures are prepared by rapid solidification process in which both the components are in crystalline in nature in order to obtain physical mixtures. These are completely miscible in all proportions in liquid state but partially miscible in solid state. Examples are urea, organic acids etc.

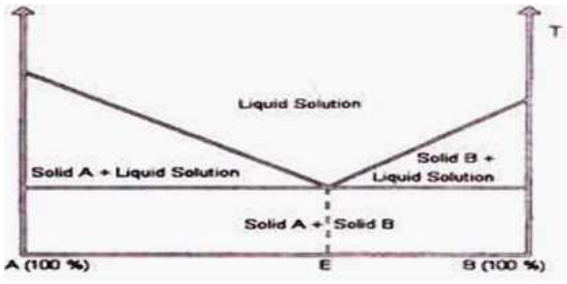

Figure 2: Eutectic mixtures phase diagram

Amorphous precipitation in crystalline matrix: The solute molecules are molecularly dispersed or irregularly dispersed in an amorphous solvent or carrier [17]. The important parameter which is considered in these solid dispersions is glass transition temperature (T_g) of the carrier.

Solid solutions: The dissolution of the solid solutions is mainly depends on the dissolution rate of the matrix. They are just like homogeneous liquid solutions but number of components may vary. Solid solutions are again further classified into two types.

- Based on the miscibility
- Based on the distribution of solute molecule in the solvent
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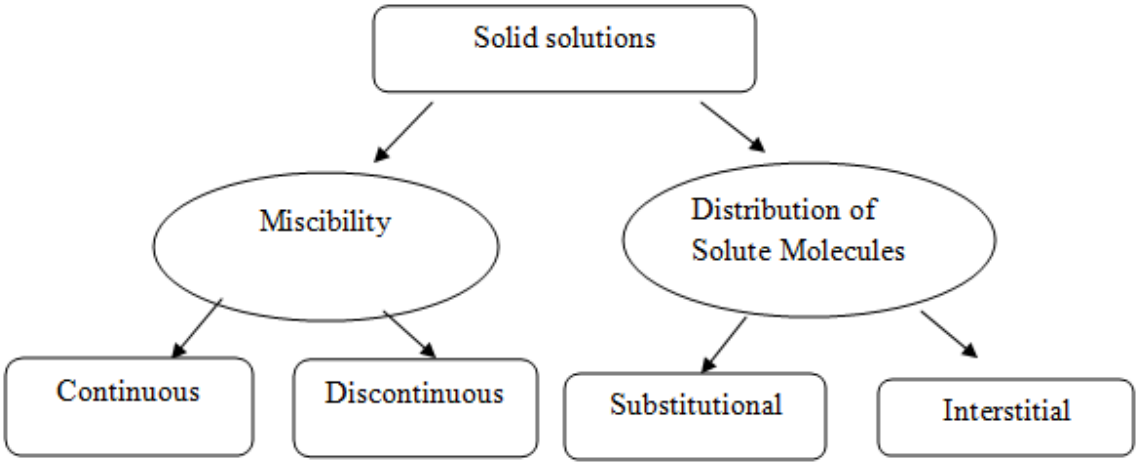

Figure 3: Classification of solid solutions of solid dispersions

Based on miscibility:

Continuous solid dispersions: The components which are present in these systems are completely miscible in all proportions at all conditions. This indicates that adhesive forces of interactions between the two components are more dominant than cohesive forces of interaction between the individual components.

Discontinuous solid dispersions: in these dispersions, the solubility of each of the component in the other component is limited. These solid dispersions can be prepared by using ternary phase diagrams which gives the information about the phase solubility studies of drug and carrier. When the mutual solubility of the two components exceed 5%then it represent the solid dispersions.

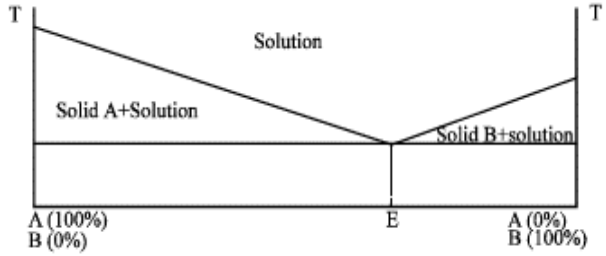

Figure 4: Phase diagram of continuous solid dispersions

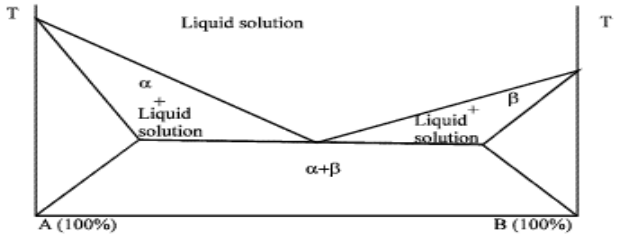

Figure 5: Phase diagram of discontinuous solid dispersions

Based on distribution of solvent molecules in solvent:

Substitutional solid dispersions: In these solid dispersions, the solute molecules are distributed in the interstitial spaces between the crystalline structures of the carrier which is dissolved in suitable solvent.

Interstitial solid dispersions: In these dispersions, the dissolved molecules occur in the interstitial spaces between the solvent molecules in the crystalline lattice. In case of substitutional the relative molecular size is considered while in this the dissolved molecular state has a diameter of about 0.6Å of the solvent molecule.

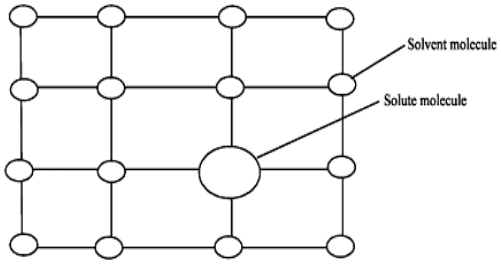

Figure 6: Substitutional Solid Dispersions

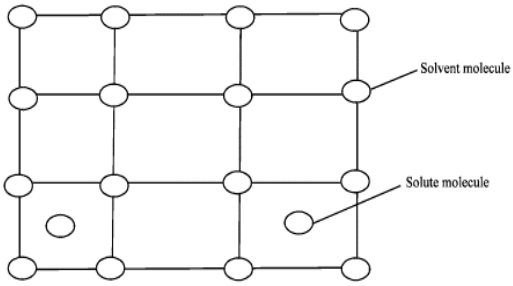

Figure 7: Interstitial Solid Dispersions

Glass solutions and suspensions: Chiou and Riegelmann were first studied the topic of glass solution and suspensions. A glass solution is a homogenous system in which a glass or a vitreous form of the carrier solubilized drug molecule whereas in case of suspensions the solute molecules are diapered in carrier.

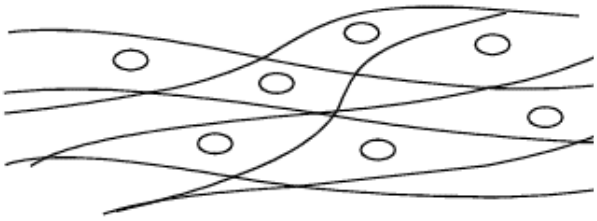

Figure 8: Glass solutions

OTHER CATEGORIES:

Non self-emulsifying solid dispersions: In these systems both amorphous and crystalline substances are used. The carriers which are used in these dispersion are comes under the category of non self-emulsifying agents. Out of the amorphous and crystalline substances, amorphous materials are more preferable because of their maximum solubility. NSESDs are prepared by using different methods like melting method, solvent method depending on the physicochemical properties of the drug and carrier.

Self emulsifying solid dispersions: Surface active agents or self emulsifying agents are used as carriers. In these systems the drugs are dissolved in molten carrier which is melted at higher temperature. As surface active agents are amphiphilic in nature that it contains both hydrophilic and hydrophobic groups in their structure they usually improve the solubility of the drug by altering the surface or interfacial free energy of the solvent system then by adsorbing of drugs at the interfaces of the system.

Table .2: Types of solid dispersions [19]

S. NO.	SOLID DISPERSION TYPE	MATRIX	DRUG	REMARKS	NUMBER OF PHASES
I	Eutectics	Crystalline	Crystalline	The first type of solid dispersion prepared	2
II	Amorphous precipitation in crystalline matrix	Crystalline	Amorphous	Rarely encountered	2
III	Solid solutions: Continuous solid solutions	Crystalline	Molecularly dispersed	Miscible at all proportions; never prepared	1
	Discontinuous solid solutions	Crystalline	Molecularly dispersed	Partially miscible, the drug is present in molecularly dispersed form	2
	Substitutional	Crystalline	Molecularly dispersed	Molecular diameter of drug (solute) differs less than 15% from the matrix (solvent) which results in the substitutional of drug and matrix can be continuous or discontinuous	1 or 2
	Interstitial solid solutions	Crystalline	Molecularly dispersed	Drug (solute) molecules diameter less than 59% of the matrix(solvent) usually limited miscibility and discontinuous	2
IV	Glass suspensions	Amorphous	Crystalline	Particle size of the dispersed phase dependent on cooling or evaporation rate obtained after crystallization of drug in amorphous matrix	2
	Glass suspensions	Amorphous	Amorphous	Particle size of dispersed phase dependent on cooling or evaporation rate	2
	Glass solutions	Amorphous	Molecularly dispersed	Requires miscibility or solid solubility, complex formation or evaporation during preparation	1
V	Non self-emulsifying solid dispersions	Amorphous or Crystalline	Amorphous or Crystalline	The matrix (carrier) which are used in these dispersions are non self-emulsifying agents and the formation of solid dispersion is mainly depends on physicochemical properties of drug and matrix	2
	Self-emulsifying solid dispersions	Amphiphilic in nature	Crystalline or Amorphous	In these formulations amphiphilic carriers (Surfactants) are used which are usually prepared by employing heat (i.e., Melting method)	2

ADVANTAGES [18]:

- It improves the solubility of the water insoluble drugs (class II).
- Improves the absorption efficiency and therapeutic efficacy is attained.
- It usually reduces the adverse effects on reduction in the dose of the drug.
- They can be used to produce rapid action by formulating them as fast dissolving agents
- Due to increase in dissolution rate and absorption presystemic metabolism can be reduced.
- Used for formulation of both sustained and fast release formulations of poorly soluble drugs.

DISADVANTAGES [19]:

- High loads of carriers are used in the formulation
- Reproducibility of physicochemical properties of the drug cannot be regained.
- Physical and chemical instability can be observed due to the modification of basic structure of drug
- Handling of the solid dispersions may be difficult due to its tackiness property.
-

METHOD OF PREPARATION:

Numerous technologies have been introduced for enhancement of poorly water soluble drug and these includes

1. Solvent method
2. Fusion method
3. Hot melt extrusion method
4. Super critical fluid method
5. Melt agglomeration method
6. Spray drying
7. Kneading method
8. Effervescent method
9. Electro spinning method
10. Direct capsule filling

11. Use of surfactants
12. Co grinding method
13. Melt dose
14. Quasi-emulsion solvent diffusion method
15. Adsorption on insoluble carriers

Solvent method: This method is also known as solvent evaporation method. It was first developed by Tachibama and Nakashmara in 1965. The main steps involved in this method are solubilization of drug and carrier in a suitable solvent, after complete solubilization the solvent is removed which results in the formation of amorphous substance. This method is mainly applicable for the thermolabile substances and the limitations are incomplete removal of solvent may result in stability problems [20]. Singh Chatter *et al.*, reports the solubility of pioglitazone hydrochloride is increased by using different concentrations of PVP K30 when compared with the variable concentrations of PEG 6000 which are prepared by employing solvent evaporation method [21]. Other example is glimepride [22].

Fusion method: This method is also known as melting method.The main steps involved in this method are initially the mixtures of drug and carriers are prepared and are melted by subjecting to the high temperatures (i.e., beyond the melting point of the carrier) followed by rapid cooling results in the solidification of molten material or melt in an ice bath with continuous stirring. For better results the molten mixture is stored in a desicator for one or more days by maintaining the appropriate conditions (ambient temperature) before size reduction and sieving [23]. This method is simple and economical. Oxidative drugs are mainly used for this process due to utilization of nitrogen gas or carrier. The main drawbacks of this method are not applicable for thermolabile drugs. Sometimes phase separation may occur due to exposing the mixture to high temperatures. Bhise *et al.*, studied the effect of polymers on enhancement of solubility of telmisartan by using various concentrations of poloxamer 407, gelucire 43/01, HPMC E4, PVP K30 and PEG 6000 by using fusion method. He concluded that the solubility of telmisartan is increased by increasing the concentration of polymer. Out of these polymers, poloxamer 407 has shown the better results [24]. Other examples are terbinafine hydrochloride [25], glimepride [26].

Hot melt extrusion method: In this method, intense mixing of drug and carrier can be achieved by using a special device called extruder. The powder blend is transferred to the die cavity by rotating screw through a heating barrel of extruder which produces the product of desired uniform shape and it is cutted by hot blade which is present at the end of the extruder [27]. The main advantages of this method are continuous process of production can be achieved and this does not require any type of solvent. Stability problems will be less. Ritesh A. Fule *et al.*, observed that the formulations which are prepared by soluplus-Lutrol showed better release when compared with the other mixtures of soluplus-PEG 400, Soluplus-Lutrol F68 and Pure solutol of artemether which are prepared by hot melt extrude technique [28].

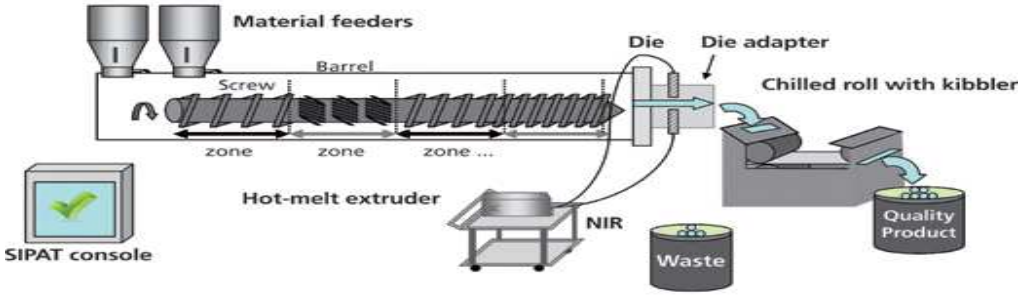

Figure 9: Schematic diagram of hot melt extrusion method

SUPERCRITICAL FLUID METHOD: This method was developed by ferro corporation which utilizes the super critical fluids usually enhance the solubility of the poorly water soluble drugs. The main components of this system are mixing vessel (for solubilizing the drug and carrier in super critical fluid), spray nozzle and expansion vessel. The drug and carrier is dissolved in supercritical fluid and is sprayed into expansion chamber by usingspray nozzle with low pressure to produce melt [29]. This method is also known as rapid expansion of supercritical solution (RESS). The most commonly used supercritical fluid is carbondioxide because of its desired properties like low

temperature (31.3℃) and low pressure (73.8 barr), nontoxic, inexpensive and non-inflammable in nature. Xuezhi yin *et al*., reported the mixtures which are prepared by super critical fluid method shows greater oral bioavailability when compared with that of the marketed product sporonax® of itraconazole [30].

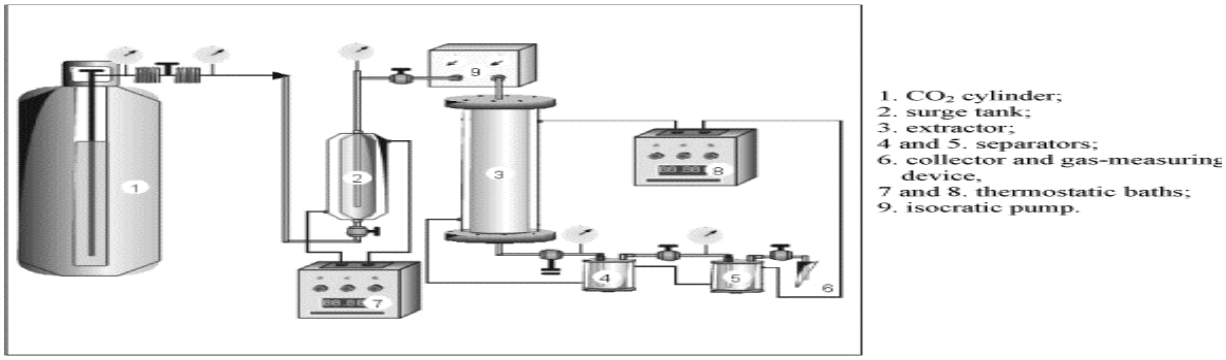

Figure 10: Schematic diagram of super critical fluid recrystallization method

MELT AGGLOMERATION METHOD: In this technique, thermal treating of drug and carrier is achieved for the production of the molten mixture beyond their melting point and the molten dispersion is sprayed into high shear rate mixtures to obtain the desired particle size and then it is dried [31]. The critical parameters which are to be considered are particle size, speed and rate of spraying and type of carrier and selection of carrier and the carrier is also acts as binder for the formation or agglomeration of drug particles.

SPRAY DRYING: The main excipients of this process are bulking agents like mannitol and lactose (to produce the desired weight), super disintegrants like sodium starch glycolate, cross povidone and croscaramellose (for rapid disintegration of the tablet, acidic agents like citric acid, tartaric acid etc. and basic agents like carbonates and bicarbonates (to produce frizzy sensation by the evolution of Co_2 gas). The drug which is produced by spray drying technique is highly porous in nature. The mixture of API and excipients are properly blended and compressed into tablet. The tablet was disintegrated with in 20 sec when it comes in contact with saliva. In this technique the important step is atomization of the particles which plays an important role in the resultant of porous structure of the materials [32]. Some of the examples of drugs of this technique where the solubility is enhanced by this technique are tinidazole [33], fluconazole [34] and ritonavir [35].

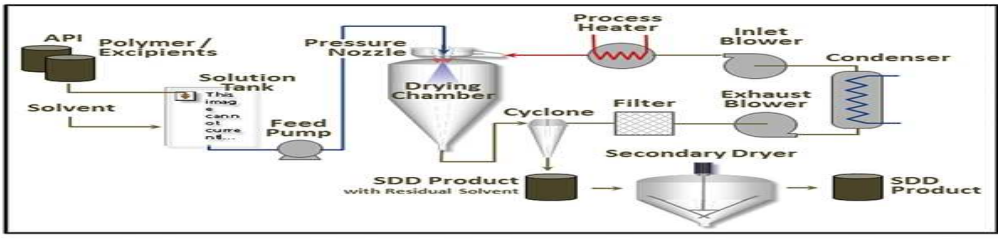

Figure 11: Schematic overview of spray drying process

KNEADING METHOD: In this method, suitable proportions of drug and carrier are taken in a mortar to that organic volatile solvents are added. Kneading process can be done for about 30 mins and it is dried until the solvent completely evaporates. For better results, the mixture is placed in desicator for the complete removal of solvent [36]. Ganesh chaulang *et al*., reported that the furosemide tablets formulated with sodium starch glycolate by kneading method showed better results when compared with marketed tablets [37].

EFFERVESCENT METHOD: The combination of utilization of organic acids and bases with poorly soluble drugs yields effervescent solid dispersions and these substances will evolve carbondioxide when comes in contact with the aqueous phase. These are mainly applicable in formulation of fast dissolving tablets and sustained release

tablets [38]. Examples of basic substances are carbonate and bicarbonates and for acidic substances are citric acids, succinic acids etc.

ELECTROPINNING METHOD [39]: In this method, the enhancement of poorly water soluble drugs can be achieved by utilization of electrical potential which results in the formation of encapsulated fibers. When adesired amount of potential is applied across the solution of drugpolymer it results in the formation of fibers of sub micron range due to domination of electrical force at the interface when compared with the interactive forces (i.e., surfacetension) of drug and carrier. The size of the fibers is mainly depends on feed size, dielectric constant and electrical strength. The optimum electrical potential which is about 5 and 30 kv

DIRECT CAPSULE FILLING [40]: In this method, the obtained liquid melt (solubilized drug) is directly filled into hard gelatin capsule. The chemical structure of the drug cannot be affected.

USE OF SURFACTANTS [41]: This method is mainly applicable for the enhancement of poorly water soluble drugs by using surfactants. These mainly act by decreasing the interfacial tension of the hydrophobic drug and results in the solubilization of drug.

CO-GRINDING METHOD: In this method, co-solvents are used. The main steps involved in this method are initially the drug is dissolved in a suitable solvent and later addition of polymer (carrier) takes place. The whole mixture is heated by applying low temperature for the evaporation of the solvent. Based on the amount of carrier used the release profile of drug from the carrier molecule can be altered [42]. Keerthi *et al*., reported that the solid dispersions of clopidogrel bisulphate prepared by co-grinding method by using different carrier concentration of mixtures of cornstarch lactose and by individual concentrations of cornstarch and dextrose [43]. Out of these, the solid dispersions which are prepared by the cornstarch-lactose mixture showed better solubility when compared with other two formulations. Another example is formulation of furosemide [44] preparations by co-grinding method.

MELT DOSE TECHNOLOGY: This technology is a combination of the methods which uses both solvent method and fusion method in which the drug is incorporated in a molten or meltable vehicle and the obtained mixture is sprayed and dried by using spray drying or by fluid bed evaporator in case of large scale and pilot scale respectively. The obtained granules are directly compressed into tablet without any addition of excipients except lubricants for promoting the flow properties [16]. This technology can be applied for the formulation of enteric coated, controlled release and fast release tablets by employing desired proportions of the carriers. The major limitation of this technology is that the whole process must be performed under controlled conditions to prevent the oxidation of oxidisible substances of the formulation.

QUASI-EMULSION SOLVENT DIFFUSION METHOD [16]: It was developed by kawashima who employed this technique in the preparation of controlled release microspheres. The enhancement of the solubility of the drug is attained by the formation of quasi crystals by dissolving in suitable solvents. They are three types of solvents are used in this technique one solvent isgood solvent which usuallysolubilized the drug and another solvent is poor solvent in which the drug is immiscible in nature. A bridging solvent is another solvent which plays an important role in the formation of quasi crystals of the drug as the drug shows miscibility with it. In this method, the drug is dissolved in both good solvent and bridging solvent. Due to the interactions between these solvents the drug molecules which are in solution state is precipitated by "salting out" up on rapid stirring and then the crystals are collected and dried. Ujwala *et al*., reported that the solubility of loperamide hydrochloride was increased by Eudragit agglomerates which are prepared by quasi emulsion solvent method [45].

ADSORPTION ON INSOLUBLE CARRIERS [46]: These dispersions are referred as surface solid dispersions. In this method, the drug substance is dissolved in a suitable solvent and it is coated on supporting material or carrier. After complete evaporation of solvent it results in improving the interactive forces between the drug and carrier and finally it is crushed and formulated into desired formulation.

CONCLUSION

Extensive research has been going in the area of solid dispersions to improve the bioavailability of the poorly soluble drugs in these days. The researchers have been using the different polymers to enhance the solubility of drugs. Proper selection of formulation method and carrier are mainly depends up on the physicochemical properties

of the targeted drug (poorly soluble drug). This technology is also highly potential to formulate controlled release dosage forms as the carriers may enhance the delay release. The major limitation of solid dispersion is the scale up process in order to avoid this problem several optimized techniques are developed by the manufacturers to produce easily scalable products.

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REFERENCES

[1] L Shargel, S Wu-Pong, A Yu. **"**Applied bio pharmaceutics & Pharmacokinetics", 6th Edition, McGrawHill, Singapore, **2012,** 365.
[2] VZ Bhut; AB Prajapati; KN Patel; BA Patel; PA Patel, *IJPRS*, **2009**, 1(2), 490-498.
[3] S Singh; BR Singh; L Yadav, *Int. J. of Pharm & Life Sci*., **2011**, 2(9), 1078-1095.
[4] NV Kumar; A Gupta; H Prasad; A Roshan; SP Srivastava; V Chandra, *J. Pharmaceut. Biomed*, **2014**, 2(2), 174-184.
[5] US Ingle; PD Gaikwad; VH Bankar; SP Pawar, *IJRAP*, **2011**, 2(3), 751-757.
[6] V Tantishaiyakul; N Kaewnopparat; S Ingkatwoinwong, *Int. J. Pharm*, **1999**, 181, 143-151.
[7] RN Sharma; M Basha, *Powder technology*, **2013**, 237, 406-414.
[8] S Patro; AAChoudhary, *International Journal of Pharmaceutical Sciences*, **2005**, 67, 334-331.
[9] A Bharati; YU Jaganadhrao; BS Lakshmi; KNV Deepthi; MCH Phanindra; BS Prasad, *International Journal of Pharma Research and Review*, **2014**, 3(3), 34-47.
[10] R Kiroj; R Bajracharya; AShrestha; P Thapa, *JPSR*, **2014**, 5, 127-139.
[11] JT Carstenen. "Advanced Pharmaceutical Solids", Marcel Dekker; New York: **2001**. 186.
[12] J Kaur; G Aggarwal; G Singh; AC Rana, *Int J Pharm Pharm Sci*, **2012**, 4(2), 47-53.
[13] AS Pankaj; DJ Prakash, *IJPRBS*, **2013**, 2(3), 114-143.
[14] B Kapoor; R Kaur; S Kour; H Behl; S Kour, *Int J Recent Adv Pharm Res.* **2012**, 2(2), 1-16.
[15] R Pahwa; U Kataria; AC Rana; R Rao; S Nanda, *IJPSR*, **2015**,6(2), 510-520.
[16] M Joshi; G Tiwari; R Tiwari; S Pandey; P Pandey; AK Rai, *Current Pharma Research*, **2012**, 2(4), 668-677.
[17] R Kaur; DJW Grant; T Eaves, *Journal of PharmaceuticalSciences*. **1980**, 69, 1321-1326.
[18] AK Dixit; RP Singh; S Singh, *International Journal of Research in Pharmaceutical and Biomedical Sciences.* **2012**, 3(2), 960-966.
[19] A Kalia; M Poddar, *Int J Pham Pharm Sci*, **2011**, 3(4), 9-19.
[20] RM Patil; AH Maniyar; MT Kale; AM Akarte; DT Bariskar, *International Journal of Pharmaceutical sciences review and research.* **2011**, 8(2), 66-73.
[21] C Singh; P kumar, *International Journal of pharmaceutical, chemical and biological sciences*, **2013**, 3(2), 350-359.
[22] A Mehta; S Vasanti; T Rajeev; S Anshuman, *Current Trends in Biotechnology*, **2009**, 3(1), 76-84.
[23] ND Dixit; SK Niranjan, *WJPPS*, 2014, 3(5), 238-257.
[24] S Bhise; D Mathure; MVK Patil; RD Patankar, *Int J Pharm & Life Sci*, **2011**, 2(8), 791-796.
[25] AK Prasad; N Narayanan; G Rajalakshmi, *International Journal of Pharmaceutical Sciences Review and Research*, **2010**, 3(1), 130-134.
[26] B Gill; T Kaur; S Kumar; GD Gupta, *Asian Journal of Pharmaceutics*, **2010**, 4(3), 212-215.
[27] YS Chan, *International Journal of Biology, Pharmacy and Allied Sciences*, **2013**, 2(12), 2415-2442.
[28] Artemether-Soluplus hot-melt extrudate solid dispersion system for solubility and dissolution rate enhancement with amorphous state characteristics. [Internet]. [Cited 14th march **2016**]. http://dx.doi.org/10.1155/2013/1511432.
[29] Sk Das; S Roy; K Yuvaraja; J Khanam; A Nanda, *IJPPT*, **2012**, 1(1), 37-46.
[30] X Yin; SL Daintree; S Ding; MD Ledgar; B Wang; W Zhao; J Qi; W Wu, *Drug Design, Development Therapy*, **2015**, 9, 2801-2810.
[31] VW Tukaram, *IJAPBC*, **2013**, 2(1), 152-160.
[32] S Kumar; R Malviya; PK Sharma, *African J Basic & Appl Sci*, **2011**, 3(4), 116-125.
[33] C Pukhraj; T Amit; JK Amit, *International Journal of Pharmaceutical Studies and Research*, **2015**, 3(2), 1-5.
[34] SS Shinde; MV Patil; AS Shete; JL Disouza; P Atpadikar, *International Journal of Drug Delivery*, **2013**, 5(3), 323-330.
[35] SS Poddar; SU Nigade; DK Singh, *Scholars Research Library: Der Pharmacia Lettre*, **2011**, 3(5), 213-223.

[36] PRK Choudhary; RK Shankar; M Subbalakshmi, *JGTPS*, **2014**, 5(2), 1612-1623.
[37] G Chaulang; P Patel; S Haridkar; M Kellar; A Bhosale; S Bhise, *Tropical Journal of Pharmaceutical Research*, **2009**, 8(1), 43-51.
[38] PD Patil; SP Bakliwal; NA Gujarithi; BR Rane; SP Pawar, *International Journal of Pharmaceutical sciences*, **2013**, 4(1), 3683-3709.
[39] S Dhiman; P Kaur; S Arora, *Drug Invention Today*, **2012**, 4(10), 478-486.
[40] PD Kumar; V Arora, *JPSI*, **2012**, 1(3), 27-34.
[41] N Singh; D Allawadi; S Singh, *International Journal of Pharmaceutical and Chemical Sciences*, **2013**, 2(2), 1092-1101.
[42] PS Argade; DP Magar, RB saudagar, *J Adv Pharm Edu & Res*, **2013**, 3(4), 427-439.
[43] M Keerthi; N Ramarao; SM Aruna; LJ Prasanna, *Asian Journal of Research in Pharmaceutical Sciences*, **2014**, 4(4), 165-168.
[44] M Reza siahi-shadbad; S Ghanbarzadeh; M barzegar-jalali; H Alrezataherpoor; G Mohmmadi; A Barzegar-Jalali; K Adibkia, *Advanced Pharmaceutical Bulletin*, **2014**, 4(4), 391-399.
[45] BR Ujwala; VK Redasani; NK Sachin, *Int J Pharm Pharm Sci*, **2013**, 5(2), 409-419.
[46] B Yadav; YS Tanwar, *J Chem Pharm Res*, **2015**, 7(2), 965-978.