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Solid Dispersion and Its Manufacturing Techniques to Improve Bioavailability of Poorly Water-Soluble Anticancer Drugs

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ABSTRACT

The report of Technology Catalyst International reveals that nearly 40 percent of novel chemical entities including anticancer drugs face the challenges of poor aqueous solubility. For an orally administered drug, its rate of drug release and solubility are the two essential factors that could influence the absorption and the bioavailability of drugs. The anticancer drugs on behalf of safety and effectiveness can be categorized into Biologic anticancer drugs and non- biologic anticancer drugs. The Biologics includes monoclonal antibodies, which are administered intravenously, because of large molecular weight, whereas non-biologics involves low molecular weight drugs, administered orally. It is evident that the intravenous administration offers quick response and cent percent bioavailability, but at the same time, patient compliance is less because of invasion and availability of an expert to inject, moreover intravenous administration has some drawbacks like hypersensitivity, neurotoxicity, etc. However oral mode of drug administration is always a convenient and most preferable means for patients, offers good patient compliance as there is no pain, cost-effective and safer. The most frequent problems with novel chemical entities and anticancer drugs are poor aqueous solvability and less rate of drug release. Numerous options could opt to overcome this issue like particle size reduction, solid dispersions, nanoparticles, crystal engineering, etc. Solid dispersion has wide acceptance and considered a successful method in formulation and development.

INTRODUCTION:

In Modern Era, Cancer is the most challenging issue and the major cause of death and its treatment is complicated and expensive too. The best possible treatments of cancer are Surgery done by an expert oncologist, chemotherapy which comprises the application of anticancer drugs and Radiotherapy performed by expert radio oncologist. [1]

The prime objective of cancer treatment is to kill cancerous cells maximally, at the same timeless harm to surrounding non-cancerous cells, depending upon the severity the patient can be subjected to single therapy or the blend of therapy e.g., Hwang et al, [2] for the treatment of cancer suggested blended therapy that was photodynamic therapy and anti-cancer immunity. In the case of solid tumors, surgery is a good option and a first-line treatment for the majority of tumors done by an expert oncologist. The consequences may be tumor may not be in a condition to remove fully and there may be some post-operative complications. The radiotherapy emphasis on killing cancer cells as much as possible but a major drawback of this therapy that it may exert harm to nearby tissues moreover sometimes it is required to deliver at the daily or weekly basis that may lead to patient inconvenience also there is excessive loss of hairs, keeping in mind all these issues, use of oral anticancer drugs for the treatment of local as well as metastasize cancers have more priority. Moreover, chemotherapy has the potential to destroy cancerous cells in the entire body and elimination of microscopic disorders associated with tumors that may not be identified by the surgeon. The amalgamation of chemotherapy with other therapy is one of the best options for cancer treatment. Tumour targeted drug delivery systems and control drug delivery systems are the two essential strategies for cancer treatment ensuring fewer side effects and more specific treatment.

Oral Drug Delivery System

The oral route of drug administration is always a preferential and most convenient route, unlike i.v. infusion no expert is required to administer drug and can be taken at home. Oral delivery usually doesn't cause any discomfit. The concentration of anti-cancer drugs can be preserved in cancer cells or tissues. In oral drug delivery, the required therapeutic concentration of drug in the systemic circulation is drug solubility dependent. The drug should be able to dissolve in the gastrointestinal tract fluid followed by permeation through the GI tract membrane to blood to exert its effect. The report of Technology Catalyst

International reveals that nearly 40 percent of novel chemical entities including anticancer drugs face the challenge of poor aqueous solubility [3-5], because of poor aqueous solubility drug is not able to absorb fully in the GI tract, results in insufficient Bioavailability and variation in inter as well as intra pharmacokinetic parameters.

Biopharmaceutical Classification System

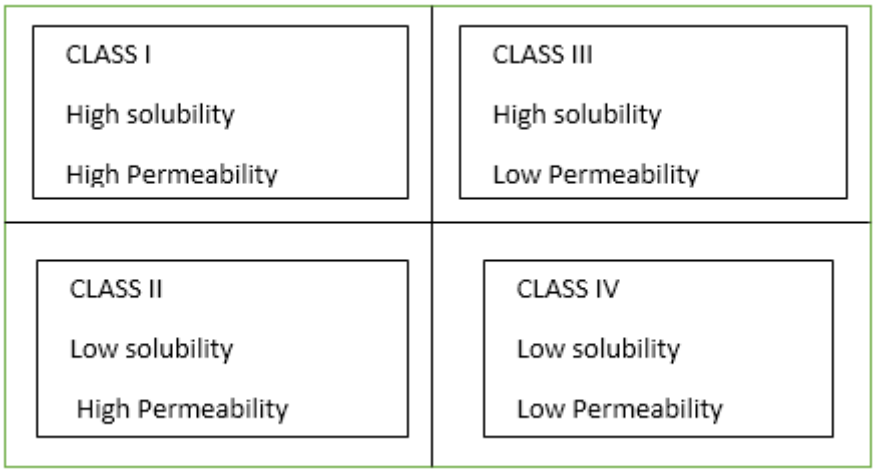

Figure No. 1: Biopharmaceutical Classification System

BCS has categorized the drugs into four categories as mentioned in figure 1, drugs are grouped under the criteria of solubility and permeability which assist the formulator to choose drug and prepare its formulation. **[6,7]** The drug can be regarded as highly soluble when the maximum therapeutic dose is soluble in ≤250ml water media at pH ranging 1.2 – 6.8 at temperature 37±1ºC. A report of the human pharmacokinetic study can be used to analyze the permeability of drugs based on the absorption of the drug in humans. The drug is regarded as highly permeable when the absorption of drugs is ≥90% of the dose given to humans, in comparison to I.V. reference dose. The drug can also be designated as highly permeable when ≥85% of the dose given is excreted unchanged in urine or summation of the conjugative metabolite of phase II and oxidative of phase I.

The necessity of Solubility Enhancement

Following BCS the drugs falling in class II and Class IV have the issue of solubility (Figure1) and there are many anticancer that have the problem of less solubility too, maximum drugs have low aqueous solubility and their therapeutic benefits cannot be left unused Therefore it is a major challenge before researchers to enhance the solubility of poorly water-soluble anticancer drugs.

Strategies to improve Solubility and Bioavailability

Advancements in Pharmaceutical science and technology have permitted to escalate the solubility and Bioavailability of anticancer drugs. There are numerous technologies that can be employed are as Solid dispersion technique [8-10], Complexation technique [11], Micronization method [12-13], Co-Crystals [14,15} nanonization technique [16-18]. Out of all these mentioned techniques, Solid dispersion is regarded as a successful method that can be utilized for solubility enhancement.

Solid Dispersion:

In 1961, Sekiguchi and Obi designed a technique termed as Solid Dispersion through which the problem of poor bioavailability of poorly water-soluble drugs was resolved [19-20]. Solid dispersion method is a technique of adding few or more active ingredients (hydrophobic) in an inert matrix (hydrophilic) in solid stage to achieve increased dissolution rate, sustained release of drugs, change solid-state traits and increase the release of drug from the ointment, suppository bases and improves the solubility and stability.

The solid dispersion is prepared by adopting the process of mixing the hydrophobic drug in the hydrophilic polymer matrix by melting method, a solvent evaporation method, etc. The solid dispersion may be regarded as Solid-state dispersion. [21]

Classification Solid dispersion

The solid dispersion can be categorized as follows:

1. Based on Carrier system utilized **[22]**

2. Based on molecular configuration **[23]**

Solid dispersions can be stratified into three following generations based on carrier system employed.

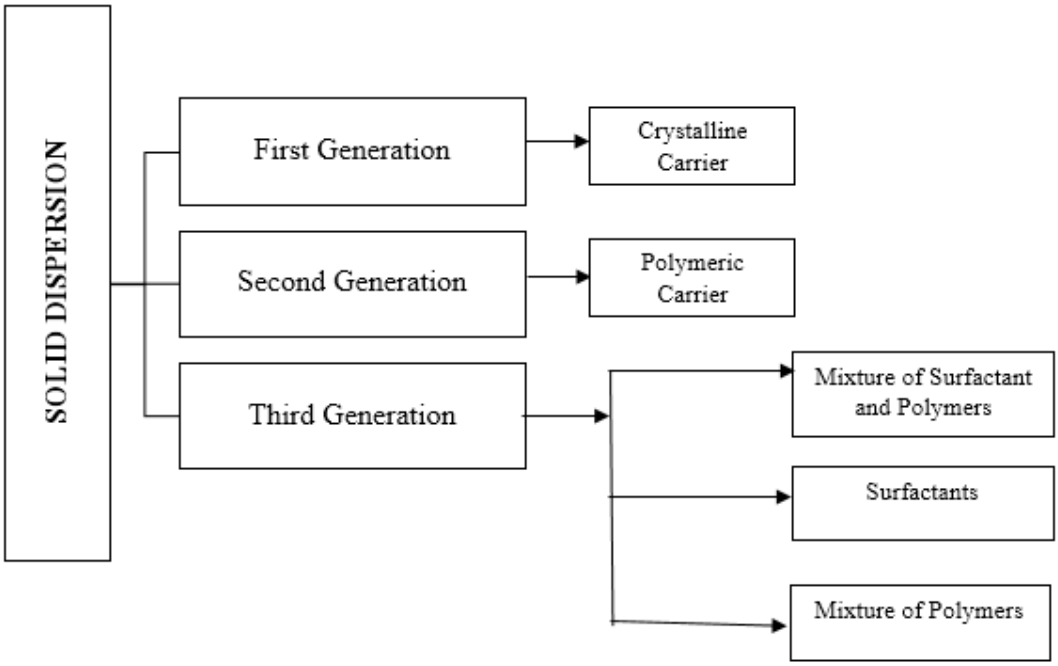

Figure No. 2: Different generations of Solid dispersions

First-generation solid dispersions: It involves the application of sugars and crystalline carriers such as urea to enhance the drug release and bioavailability**.** These were the carriers employed firstly for solid dispersion preparation. The comparative absorption study of eutectic mixture of sulfathiazole and chloramphenicol was done with a conventional form of identical drugs. [24, 25] Later on mannitol was employed as a carrier instead of the eutectic mixture by Levi [26] the prepared solid dispersion represented a marked increase in dissolution. The conclusion was drawn that the application of crystalline carriers e.g., sugars and urea leads to the formation of unstable and less drug release.

Second generation solid dispersion: The drawbacks behind first-generation solid dispersions [26] give birth to second-generation solid dispersions which involve the application of amorphous polymeric agents. It involves the application of polyethylene glycols, povidone, polymethacrylates types of synthetic polymeric agents, hydroxypropyl methylcellulose; ethylcellulose, etc. natural carriers are employed.

Third generation solid dispersions: In recent years it was observed that the application of carrier which has surface activity or surfactants can be employed in association with hydrophilic agents or alone have the capability to increase the rate of drug release and bioavailability. Hence the third generation of solid dispersion came into existence. The reason behind increases in solubility might be the adsorption of the surface-active agent over the hydrophobic drug which in turn reduces surface tension existing with solid-liquid or between two liquids. The surface-active agents that may be employed are inulin [28-29], poloxamer 407, compritol 888ATO. [30]

Based on Molecular configuration, solid dispersion may be stratified as follows:

1. **Eutectic system:** The eutectic system is a blend of two constituents that melt at a single temperature, at eutectic point (A) both the constituents X and Y were co-melted, here the melting point of the mixture was lower than each constituent melting point (X and Y).

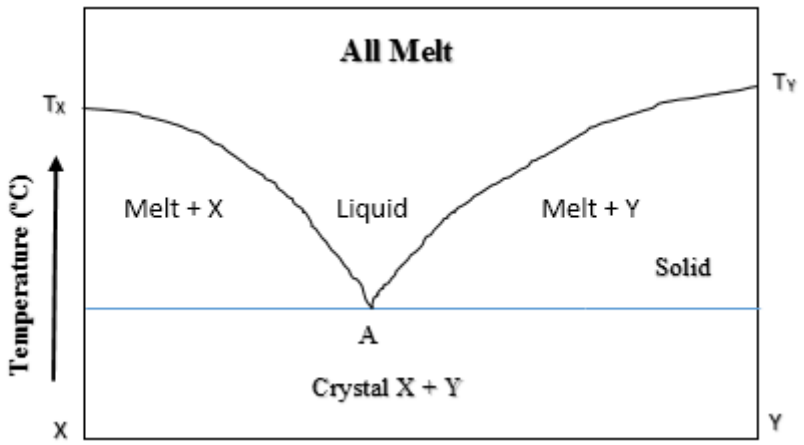

Figure No. 3: Depicts Phase diagram of eutectic composition X and Y (Drug and carrier), Eutectic point (A)

2. Solid solution System: The crystallization of two components gives rise to a homogenous single system. In solid solution, particle drug particle size is narrowed down to molecular size. Therefore, this method offers a greater dissolution rate than the eutectic mixture. As per the solubility of constituents, a solid solution can be stratified into the following categories. [31]

a) Continuous solid solution: In a solid solution, the constituents are miscible completely in the solid-state at every proportion and the bonding capacity between two constituents is more than individual constituent. [32]

b) Discontinuous solid solution: The Solubility of each constituent is restricted in the Solid solvents system.

As per the molecular size of two constituents, solid solutions may be stratified as a substitutional crystalline solid solution and interstitial crystalline solid solution**s** (Figure 4). In substitution type within the crystal lattice, the solute molecule acts as a substitute for Solvent molecule while in interstitial solid solutions within the crystal lattice the molecule has been dissolved capture the interstitial gaps between the solvent molecules. [33]

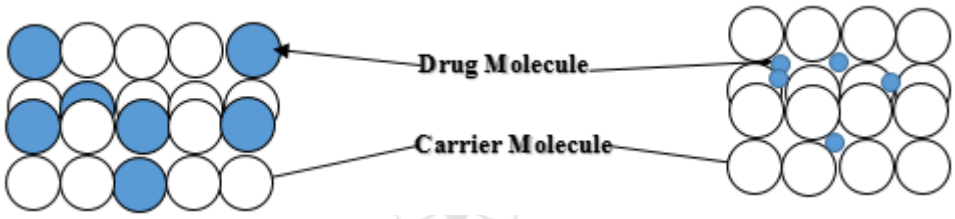

Figure No. 4: Diagrammatic structure of Solid solutions

Glass Solutions or Glass suspension

In this system the drug is solubilized in the glassy solvent, this homogenous system is termed as Glass solutions [34] while the system in which drug molecule is suspended in a glassy solvent system, termed as Glass suspension. The transparency and brittle nature below transition temperature demonstrate the glassy state of solid solution and suspension.

Manufacturing techniques of solid dispersions

The methods used for the preparation of solid dispersions can be illustrated as follows.

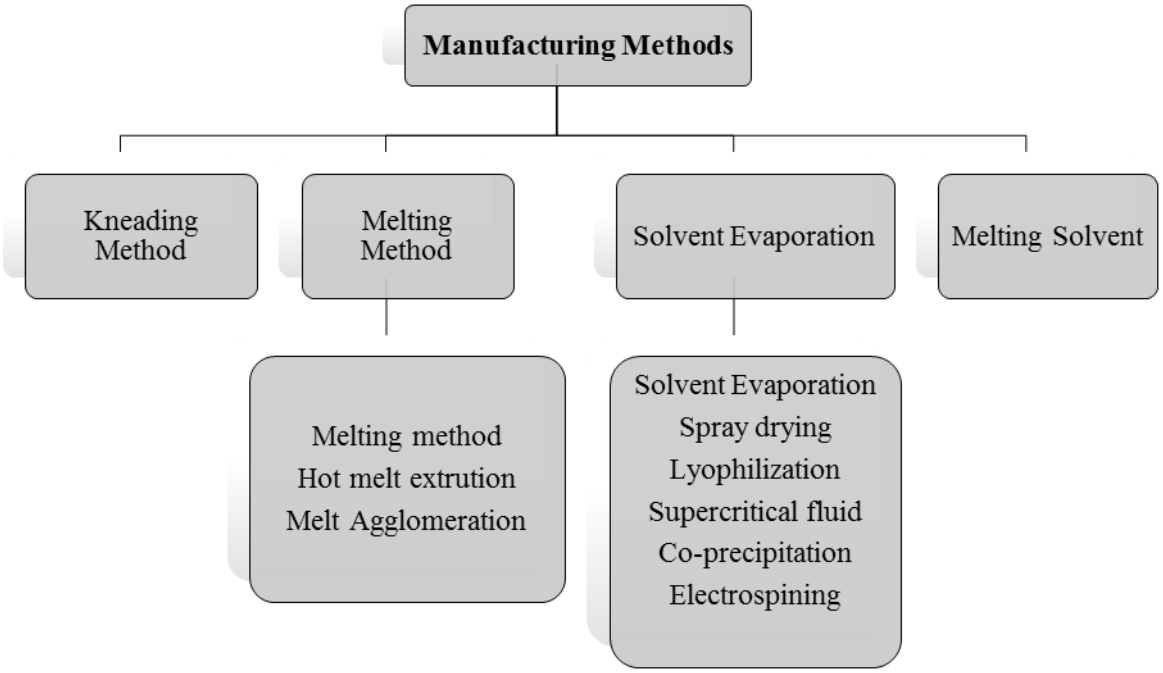

Figure No. 5: Techniques for manufacturing of solid dispersion

1. Melting Technique: The process involves heating of a physical mixture of drug and hydrophilic agents till that melt at the temperature more than its eutectic point and then the melt was followed by rapid cooling in an ice bath with continuous stirring. The obtained product was properly crushed and sieved. This method can also be employed for the solubility escalation of anti-cancer drugs. The solubility issues of prednisolone were solved by the preparation of solid dispersion by opting melting method in ratio drug: PEG 4000 (1:4) and drug: mannitol (1:7), the results have shown that there was a massive increase in drug release up to 85% in comparison of pure drug. [35] There are several drugs like Fenofibrate, paclitaxel, tacrolimus whose solid dispersion already exists which gives an idea that the extent of drug release is much greater than pure drug. [36,37]

2. Solvent evaporation technique: This technique has great importance in the Pharmaceutical industries this method is suggested for the heat-sensitive drugs that involve solubilizing drugs as well as a carrier molecule in a suitable solvent followed by evaporation. Solvent gets evaporate at a low temperature so, this process kills the chance of thermal decomposition of the drug; the drug and carrier are dissolved in the same solvent like chloroform, ethanol, etc., the obtained mass after evaporation was further pulverized and sieved. This method can opt for the escalation of solubility of many anticancer drugs like Paclitaxel [38] docetaxel [39] it was found that prepared solid dispersion has a tremendous

increase in dissolution in comparison to pure drugs. This method was found to be very good for the solubility enhancement of anticancer drugs.

3. Melt Evaporation technique: This method involves the amalgamation of solvent evaporation and hot melt method, it was initialized by Goldberg et al, [40]. In actual this technique involves dissolving in a suitable solvent followed by addition into the melt of carrier, subsequently, the mixture was allowed to evaporate till dryness. This method applies to drugs that have a high melting point.

4. Melt agglomeration technique: High shear mixtures are usually employed for the preparation of solid dispersion, in this technique drug, carrier, excipients are exposed to heating within or above the melting point range of carrier used. [41] In this method binder itself plays the role of the carrier, solid dispersion is usually prepared by heating all excipients, drug, carrier to that temperature where carrier melts. Another spray-on process can also be adapted to produce solid dispersion by drug dispersed in molten binder sprayed overheated excipient utilizing a shear mixer. To produce solid dispersion by melt agglomeration technique preferably rotary mixer is employed, due to convenience in controlling temperature. [42]

5. Hot–Melt Extrusion technique: This method involves the formation of solid dispersion without any use of solvent, hence reduces the chances of residual in the formulation. It is a widely used technique for escalation of dissolution and bioavailability of the poorly water-soluble drug. [43] This method involvement of both melting as well an extruder in extrusion method drug, polymer, and carrier and plasticizers were melted and extrude through equipment. The extruder is composed of a barrel, hopper, heated jacket, and a die. Through hopper, the drug and carrier were incorporated and ultimately extruded from the die, the shape of the final product can be controlled and in the final most step grinding is not required. The merit of this technique is that numerous shapes and designs of ophthalmic inserts, oral dosage form, implants, etc. can be produced.

Example: Tamoxifen, an anti-cancer drug solid dispersion was prepared by opting this technique using the carrier as soluplus, the observation was that the Bioavailability and dissolution were enhanced in comparison to pure drug. [44]

6. Freeze drying or Lyophilization technique: This technique is a substitute to evaporation method and it applies to thermolabile drugs which are stable in dry conditions but unstable at aqueous conditions during long storage conditions and it involves solubilizing drug and carrier in the same solvent and it is kept in liquid nitrogen till it got frozen fully to get lyophilized molecular dispersion. [45]

Example: Docetaxel an anti-cancer drug solid dispersion is prepared to utilize this technique involving poloxamer F68/P85, Solid dispersion escalates the solubility and intestinal penetrability was enhanced. [46] The solid dispersion of Exemestane prepared using Lipoid E80S/Sodium deoxycholate, Exemestane solid dispersion represented 4-6 folds increment in absorption in comparison to pure drug. [47]

7. Electrospinning technique: This technique is an amalgamation of solid dispersion and nanotechnology that involves, millimeter-scale orifice through which solid fibers can be obtained from polymeric fluid stream.[48] The merit of this technique is that it is a convenient and inexpensive method, it offers production of nanofibers and control release of biomedicine. By this technique nanofibers containing ketoprofen: Polyvinyl alcohol (1:1) was prepared. The drug release from Nanofibre was more than the only ketoprofen. [49]

8. Co-Precipitation technique: It is one of the most versatile techniques employed for the preparation of solid dispersion for enhancement of solubility and dissolution of poorly water-soluble drugs. In this method in the solution of drug and carrier, non-solvent is incorporated dropwise with continuous stirring, the micro-particles are obtained by co-precipitation of drug and carrier, ultimately microparticles were filtered and subjected to dryness, [50] i.e. the solid dispersion of anti-cancer drugs. Everolimus prepared using HPMC as a carrier in ratio (1:15) drug to HPMC the release was found to be 75% after 30 minutes hence enhancing the bioavailability of drugs. [51]

9. Spray drying technique: It is one of the most traditional, methods that are opted for drying of food and pharmaceuticals, basically the thermosensitive substances. In this method feed solution is prepared by the solubilising drug in an appropriate solvent and carrier is dissolved in water media, followed by sonication mixing of both solutions is done to obtain a clear solution. Fine droplets are prepared by spraying solution in the heating chamber, through a high-pressure nozzle to eliminate solvent and solid dispersion is obtained immediately that reduces chances of phase separation [52-53] example: Raloxifene an anti-

cancer drug prepared solid dispersion using PVP-K30 demonstrated 2.6 folds increment in bioavailability as compared to pure drug. [54]

10. Supercritical fluid method: The technique involved in this method is that supercritical fluid e.g., carbon dioxide to dissolve drug and carrier and it was sprayed via a nozzle in an expansion container at low pressure. Fast nucleation of drugs is favored by quick expansion; gives rise to solid dispersion within a short time. This method was proposed by Hannay and Hogarth in the year 1897 to obtain a nano or microparticle using a supercritical fluid.[55] The are several methods of SFC like rapid expansion from supercritical solution (RESS), Gas anti-solvent, Supercritical anti-solvent (SAS) [56], etc. The merit of this method that reduces dependency on organic solvents for the preparation of solid dispersions. The carbon dioxide is a choice of solvent in supercritical fluid technique for solid dispersion manufacturing of insoluble drugs because of its less critical temperature (31.04 ºC) and pressure (7.38 MPa), eco-friendly and less toxic, etc.[57] example: The solid dispersions of anti-cancer drugs like Letrozole, the carrier used is CO_2- methanol, solubility was observed to be increased 7.1 folds in comparison to pure drug. [58] The dissolution and absorption of solid dispersion of Oridonin made by using carrier PVP K17 were found to be 26.5 folds more than the drug itself. [59]

11. Kneading Technique: In this method there is the dispersal of the carrier in water and converted into paste form, followed by incorporation of drug and kneading is carried out perfectly. The kneaded content subjected to dryness and usually passed via a sieve. The solid dispersion of cefixime was prepared and it was found that the rate of dissolution is 6.78 times more in comparison to pre-drug that offers more bioavailability. [60]

Possible techniques for preparation of solid dispersion of anti-cancer drugs

The solid dispersion technique is a frequently used method utilize for enhancement of solubility and Bioavailability. There are numerous methods for the production of solid dispersion, out of all techniques the melting method, solvent evaporation technique, lyophilization, and supercritical fluid method are the most widely employed techniques for the manufacturing of solid dispersion. The choice of method adopts for solid dispersion preparation relies on the physicochemical attributes of anticancer drugs.

Manufacturing techniques of Solid dispersion at Lab-scale and Industrial Scale.

The methods used for solid dispersion are numerous but all methods cannot be utilized commercially. In industrial as well as in laboratory-scale melting technique and solvent evaporation methods are employed, but at the laboratory level, due to convenience, effectiveness and simplicity solvent evaporation technique is employed, freeze-drying and supercritical fluid technique are also employed. At the industrial scale, it is not convenient to prepare solid dispersion at large scale. Spray drying and freeze-drying method are preferable methods at an industrial scale. The selection of method for preparation of solid dispersion decides the success of the process, at the level of the laboratory the attributes of drug, carrier, and solvent are essential considerations for opting solvent evaporation method. However, at the industrial level, the choice of method is limited. In melting techniques, hot-melt extrusion is more common to obtain solid dispersion.

Challenges to Solid Dispersion technique

Solid dispersion is a successful technique which has been utilized for escalation of solubility of poorly aqueous solubility, however, there are many limitations like to scale up production, instability issue, there may be a problem in providing solid dispersion in capsules and tablets. However several types of research are going on to produce novel carriers that may promote stability of solid dispersion. In recent times more than one carrier is employed to prepare solid dispersion to improve stability and to reduce recrystallization. Kinetisol Dispersing technique [61] is a new method to prepare solid dispersion which involves the application of quickly revolving blades through a blend of thermal and kinetic energy, ignoring the application of heat externally that may lead to the possibility of development of novel solid dispersions in upcoming years.

Advantages of solid dispersion [62,63]

1. Solid dispersion promotes rapid dissolution of drug which leads to increase in extent and rate of drug absorption.

2. The pre-systemic metabolism of drug is reduced, that decline the drug dose.

3. Solid dispersion is a better and efficient over particle size reducing method, because this method can reduce particle size upto 2-5mm which may not be enough to enhance solubility or drug release.

4. The bioavailability can be enhanced by controlling parameters like molecular weight, Composition, Crystallanity, particle size, wettability etc.

5. The bioavailability problem can be overcome due to transformation of liquid form of drug into solid form that reduce polymorphic changes.

Disadvantages of Solid dispersion [7,63]

1. There may be decline in the solubility and dissolution of drug because of conversion of amorphous state to crystalline form or from metastable crystalline form to sable form during storage.

2. Temperature and moisture may exert degradative effect as the polymer may absorb moisture and that may lead to phase separation or crystal growth.

3. Solid dispersion may often lead to problem in handling because of tackiness.

4. There is problem in Scale -up of solid dispersions for manufacturing purposes.

CONCLUSION:

Solid dispersion technique has been regarded as a successful and versatile technique applied for enhancing solubility and dissolution poorly aqueous soluble anti-cancer drugs. This review focused on manufacturing techniques, classification of solid dispersions, various challenges, and the prospect of solid dispersion. It can be concluded that Solid dispersion is worth for enhancing solubility and bioavailability of anticancer drugs.

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