Review Article

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A Complete Review on Solid Dispersion Technology and Factorial Design.

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Abstract
Solid dispersion is one of the mostly discussed but still remained as a challenging aspect for improving dissolution rate and hence bioavailability of a poorly water soluble drugs. The focus of this review is to highlight technology and various approaches for the preparation of solid dispersion, materials used various advantages, disadvantages and future prospects with its pharmaceutical applications. This article also focuses the use of factorial design along with its types, uses and applications for the optimization of solid dispersion formulation.

Key Words
Solid dispersion; Solubility; Bioavailability; Factorial Design; Polymers; Interaction.

Introduction
More than 40% of new candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties.[1] These properties have a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity. Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties. Pharmaceutical companies have been primarily employing two strategies: rational drug design (RDD) and high throughput screening (HTS) for drug discovery. In both, lead compounds are identified according to screening in an environment in relation to biological system. RDD generally lead to compounds with higher molecular weight which ultimately result in to poorer permeability. On the other hand, HTS has led to compounds with increased lipophilicity and molecular weight; this consequently gives poorer solubility characteristics. Lipophilicity literally means loving lipid (or fat). Drugs have this property of lipophilicity too little or too much is a bad thing. When this property expressed as Log P gets above about the drug is getting too lipophilic.[2] The poor solubility and low dissolution rate of poorly water soluble drugs in the aqueous gastro-intestinal fluids often cause insufficient bioavailability. Especially for class II substances according to the Biopharmaceutics Classification System (BCS), the bioavailability may be enhanced by increasing the solubility and dissolution rate of the drug in the gastro-intestinal fluids.[3] The poorly soluble drug having dissolution rate too slow therefore uptake cannot be completed within the time at absorption site. If it remains in GIT for longer period may lead to decomposition of drug. There are two parameters useful for identifying poorly soluble drugs. One is its aqueous solubility should be less than 100ug/ml and another is dose: solubility ratio. Dose: solubility ratio can be defined as volume of gastrointestinal fluids necessary to dissolve the administered dose.

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Techniques of Solubility Enhancement
There are various techniques available to improve the solubility of poorly soluble drugs. Some of the approaches to improve the solubility are[4]

Physical Modifications
A. Particle size reduction
   a. Micronization
B. Modification of the crystal habit
   a. Polymorphism
   b. Nanosuspension
C. Drug dispersion in carriers
   a. Solid dispersions
   b. Complexation
D. Solubilization by surfactants
   a. Microemulsions
   b. Self microemulsifying drug delivery systems

II. Chemical Modifications
   a. Prodrug.
   b. Salt formation.
   c. liquid-solid compacts

III. Other techniques
1. Co solvency

2. Hydrotrophy
3. Solubilizing agents
4. Nanotechnology approaches
5. PH adjustment:
6. Microemulsion:

Definition and Types of Solid Dispersions

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, and enhanced release of drugs from ointment and suppository bases, and improved solubility and stability.

Types of solid dispersions

a) **Simple eutectic mixture**: An eutectic mixture of a sparingly water soluble drug and a highly water soluble carrier may be regarded thermodynamically as an intimately blended physical mixture of its two crystalline component. increase in surface area is mainly responsible for increased rate of dissolution. This led to a conclusion that the increase in dissolution was mainly due to decreased particle size.

b) **Solid solutions**: Solid solutions consist of a solid solute dissolved in a solid solvent. A mixed crystal is formed because the two components crystallize together in a homogenous one-phase system. Hence, this system would be expected to yield much higher rates of dissolution than simple eutectic systems.

c) **Glass solution of suspension:** A glass solution is a homogenous system in which
a glassy or a vitreous of the carrier solubilizer drug molecules in its matrix. PVP dissolved in organic solvents undergoes a transition to a glassy state upon evaporation of the solvent.

d) **Compound or complex formation:** This system is characterized by complexation of two components in a binary system during solid dispersion preparation. The availability of the drug from the complex is dependent on the solubility dissociation constant and the intrinsic absorption rate of the complex.

e) **Amorphous precipitation**: Amorphous precipitation occurs when drug precipitates as an amorphous form in the inert carrier. The higher energy state of the drug in this system generally produces much greater dissolution rates than the corresponding crystalline forms of the drug.

Methods of preparation of solid dispersions: [5,6]

1) Melting method: [7]

The melting or fusion method, first proposed by Sekiguchi and Obi involves the preparation of physical mixture of a drug and a water-soluble carrier and heating it directly until it melted. The melted mixture is then solidified rapidly in an ice-bath under vigorous stirring. The final solid mass is crushed, pulverized and sieved. Appropriately this has undergone many modifications in pouring the homogenous melt in the form of a thin layer onto a ferrite plate or a stainless steel plate and cooled by flowing air or water on the opposite side of the plate. The main advantages of this direct melting method are as follows.

Advantages

1) Its simplicity and economy.
2) In addition, a super-saturation of a solute or drug in a system can often be obtained by quenching the melt rapidly from a high temperature. Under such conditions, the solute molecule is arrested in the solvent matrix by the instantaneous solidification process. The quenching technique gives a much finer dispersion of crystallites when used for simple eutectic mixtures.

Disadvantages

However many substances, either drugs or carriers, may decompose during the fusion process which employs high temperature. It may also cause evaporation of volatile drug or volatile carrier during the fusion process at high temperature. Some of the means to overcome these problems could be heating the physical mixture in a sealed container or melting it under vacuum or in presence of inert gas like nitrogen to prevent oxidative degradation of drug or carrier.

2) Solvent method: [7,8]

In this method, the physical mixture of the drug and carrier is dissolved in a common solvent, which is evaporated until a clear, solvent free film is left. The film is further dried to constant weight.

Advantages

The main advantage of the solvent method is thermal decomposition of drugs or carriers can be prevented because of the relatively low temperatures required for the evaporation of organic solvents.

However, some disadvantages are associated with this method such as

1) The higher cost of preparation.

2) The difficulty in completely removing liquid solvent.
3) The possible adverse effect of traces of the solvent on the chemical stability of the drug.
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form.
6) In addition, a super saturation of the solute in the solid system cannot be attained except in a system showing highly viscous properties.

3) Melting solvent method (melt evaporation):[7]

It involves preparation of solid dispersions by dissolving the drug in a suitable liquid solvent and then incorporating the solution directly into the melt of polyethylene glycol, which is then evaporated until a clear, solvent free film is left. The film is further dried to constant weight. The 5 –10% (w/w) of liquid compounds can be incorporated into polyethylene glycol6000 without significant loss of its solid property. It is possible that the selected solvent or dissolved drug may not be miscible with the melt of the polyethylene glycol. Also the liquid solvent used may affect the polymorphic form of the drug, which precipitates as the solid dispersion. This technique possesses unique advantages of both the fusion and solvent evaporation methods. From a practical standpoint, it is only limited to drugs with a low therapeutic dose e.g. below 50 mg.

Selection of a Carrier

The properties of the carrier have a major influence on the dissolution characteristics of the dispersed drug. A carrier should meet the following criteria to be suitable for increasing the dissolution rate of a drug.

1. Be freely water-soluble with intrinsic rapid dissolution properties.
2. Be non-toxic and pharmacologically inert.
3. Be heat stable with a low melting point for the melt method.
4. Be soluble in a variety of solvents and pass through a vitreous state upon solvent evaporation for the solvent method.
5. Be able to preferably increase the aqueous solubility of the drug and
6. Be chemically compatible with the drug and not form a strongly bonded complex with the drug [9,10,11]

Polymers Used In Solid Dispersions:

Polymers used in solid dispersions are as follows:

a) Polyethylene glycols (PEG): The term polyethylene glycols refer to compounds that are obtained by reacting ethylene glycol with ethylene oxide. PEGs whose molecular weight is above 300000 are commonly termed as polyethylene oxides.

Effect of PEG molecular weight: The dissolution rate of pure PEG decreases with increasing molecular weight. The dissolution rate of the drug in solid dispersion can be increased with an increase in molecular weight of PEG. In these cases, the rate at which the polymer dissolved dictated the rate at which the drug dissolved. Lower molecular weight PEGs melt at 37ºC in the dissolution medium prior to dissolution, further increasing the rate of dissolution. In some drug-PEG solid dispersion systems, the rate dissolution decreases with molecular weight upto a certain composition of the drug above which the trend becomes irregular.

b) Polyvinyl pyrrolidone (PVP): PVP has a molecular weight ranging from 10,000 to 700,000. It is soluble in solvents like water, ethanol, chloroform and isopropyl alcohol. PVP is not suitable for preparation of solid dispersions prepared by melt method because of it melts at a very high temperature above 275ºC, where it becomes decomposed. Effect of PVP molecular weight: The effect of molecular weight of PVP on the rate of dissolution of a drug is more consistent than for PEG. An increase in molecular weight of PVP will decrease the dissolution rate of most drugs. An increase in viscosity of PVP solution due to an increase in molecular weight decreases diffusion of drug molecules from the surface of viscous material into the dissolution medium. Lower molecular weight PVP has a short swelling time prior to dissolution resulting in an increase in dissolution rate of the polymer and drug.

c) Polymers and surface active agent combinations: The addition of surfactants to dissolution medium lowers the interfacial tension between the drug and the dissolution medium and promotes the wetting of the drug thereby they enhance the solubility and dissolution of drugs. Ternary dispersion systems have higher dissolution rates than binary dispersion systems.

d) Cyclodextrins: Cyclodextrins are primarily used to enhance solubility, chemical protection, taste masking and improved handling by the conversion of liquids into solids by entrapment.

Oral administration of cyclodextrins: Cyclodextrins play an important role in the bioavailability of poorly water soluble drugs by increasing the rate and extent

of dissolution of drug.

Cyclodextrins also have the advantages of:

a) Increasing the stability of the drug.
b) Release profile during gastrointestinal transit through modification of drug release site and time profile.
c) Decreasing local tissue irritation.
d) Masking unpleasant taste.

e) Phospholipids: Phospholipids are major structural components of cell membranes. Phosphotidylcholine was first isolated from egg yolk and brain. Its chemical name is 1,2-diacyl-in-glycero-3-phosphocholine. In phosphatidyl ethanolamine and phosphatidyl serine, the choline moiety is replaced by ethanolamine and serine respectively. Other phospholipids that occur in tissues include phosphotidyl ethanolamide (PE), phosphotidyl serine (PS), and phosphotidyl glycerol (PG). Naturally occuring lecithins contain both a saturated fatty acid and unsaturated fatty acids with some exceptions.

Advantages and Disadvantages of Solid Dispersions

Among the advantages of solid dispersions are the rapid dissolution rates that result in an increase in the rate and extent of the absorption of the drug, and a reduction in presystemic metabolism. This latter advantage may occur due to saturation of the enzyme responsible for biotransformation of the drug, as in the case of 17□ estradiol; or inhibition of the enzyme by the carrier, as in the case of morphine-tristearin dispersion. Both can lead to the need for lower doses of the drug. Other advantages include transformation of the liquid form of the drug into a solid form (e.g., clofibrate and benzoyl benzoate can be incorporated into PEG 6000 to give a solid, avoidance of polymorphic changes and thereby bio-availability problems), as in the case of nabilone and PVP dispersion, and protection of certain drugs by PEGs (e.g., cardiac glycosides) against decomposition by saliva to allow buccal absorption. The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystallinity and a decrease in dissolution rate with aging. The crystallization of ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the ritonavir capsule (Norvir, Abboft) from the market. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersions may not lend themselves to easy handling because of tackiness.[13,14,15,16]

Future Prospects: [5,6,7]

Despite many advantages of solid dispersion, issues related to preparation, reproducibility, formulation, scale up and stability limited its use in commercial dosage forms for poorly water-soluble drugs. Successful developments of solid dispersion systems for preclinical, clinical and commercial use have been feasible in recent years due to the availability of surface-active and self-emulsifying carriers with relatively low melting points. The preparation of dosage forms involves the dissolving of drug in melted carriers and the filling of the hot solutions into hard gelatin capsules because of the simplicity of manufacturing and scale up processes, the physico-chemical properties and, as a result, the bioavailability of solid dispersions are not expected to change significantly during the scale up. For this reason, the popularity of the solid dispersion system to solve difficult bioavailability issues with respect to poorly water-soluble drugs will grow rapidly. Because the dosage form can be developed and prepared using small amounts of drug substances in early stages of the drug development process, the system might have an advantage over such other commonly used bioavailability enhancement techniques as micronization of drugs and soft gelatin encapsulation. One major focus of future research will be the identification of new surfaceactive and self-emulsifying carriers for solid dispersion. Only a small number of such carriers are currently available for oral use. Some carriers that are used for topical application of drug only may be qualified for oral use by conducting appropriate toxicological testing. One limitation in the development of solid dispersion systems may the inadequate drug solubility in carrier, so a wider choice of carriers will increase the success of dosage form development. Research should also be directed toward identification of vehicles or excipients that would retard or prevent crystallization of drugs from super-saturated systems. Attention must be given to any physiological and pharmacological effects of carriers used. Many of the surfaceactive and self-emulsifying carriers are lipidic in nature, so potential roles of such carriers on drug absorption, especially on their inhibitory effects on CYP-3 based drug metabolism and p-glycoprotein-mediated drug efflux will require careful consideration. In addition to bioavailability

enhancement, much recent research on solid dispersion systems was directed toward the development of extended-release dosage forms. Physical and chemical stability of both the drug and the carrier in a solid dispersion are major developmental issues, an exemplified by the recent withdrawal of ritonavir capsules from the market, so future research needs to be directed to address various stability issues. The semisolid and waxy nature of solid dispersions poses unique stability problems that might not be seen in other types of solid dosage forms. Predictive methods will be necessary for the investigation of any potential crystallization of drugs and its impact on dissolution and bioavailability, possible drug-carrier interactions must also be investigate.

Factorial Design

Introduction

Factorial Designs are used in Experiments where the effects of different factors, or conditions, on experimental results are to be elucidated.

"Intervention studies with two or more categorical explanatory variables leading to a numerical outcome variable are called Factorial Designs."

Objective of Factorial Design:

The objective of experimental design is to obtain the maximum information with the minimum number of experiments. Performance analysis often requires that the effects of individual factors be identified, so that meaningful statements can be made about different levels of each factor. [17]

Simple Designs:

These types of designs start with a typical configuration, and vary one factor at a time. In these types of designs we study only one factor at a time, so that the effect of that factor on the experimental results can be elucidated. These are statistically not very efficient and lead to wrong conclusions if factors have interaction. [17]

Limitations of Simple design:

1. Variation due to experimental errors is ignored
2. Important parameters are not controlled
3. Effects of different factors are not isolated
4. Too many experiments are required to be conducted.[17]

Because of all these limitations a new design developed where effect of combination of factors can be determined with minimizing the number of experiments called Factorial Design

Objectives of Factorial Design

• Try to obtain the maximum amount of information about a system for a given level of available resources.

• Determine the effects of each individual input parameter.

• Determine the effects due to interactions of the input Parameters.

Definitions

Factor

"A Factor is an assigned variable such as Concentration, Temperature, Lubricating agent, drug treatment, or diet". A factor can be Quantitative or Qualitative. Qualitative Factors-E.g. Treatment, Diet. Quantitative Factors-Eg. Concentration.

Levels

- "The levels of a factor are the values or designations assigned to the factor.
- e.g. 30^0, 50^0 Temperature, 0.1 M, 0.3 M solution Concentration".
- Levels need not be numeric. Factors can be "variable data" (numbers) or "attribute data" (on/off, male/female, Ford/Subaru/Mercedes).
- For example, if we were testing two types of catalyst (say alumina and silica); we could arbitrarily designate one as "high" and one as "low".

Effects

- "The effect of a factor is the change in response caused by varying the level(s) of the factor".
- The main effect is the effect of a factor averaged over all levels of the other factors.

Interaction

- "Interaction may be thought of as a lack of "additivity of factor effects."
- Depending on the effect obtained the factors are classified as follows,

Non-interacting factors:

Impact of one factor is always irrespective of the level of another factor. E.g.

	A_1	A_2
B_1	3	5
B_2	6	8

Interacting factors

Impact of one factor depends on the level of another factor.

E.g.

	A_1	A_2
B_1	3	5
B_2	6	**9**

Design

Specifying the number of experiments and the factor-level combination of each experiment.

Response variable:

It is an outcome of experiment, typically called as a performance measure.

Advantages:

1. In the absence of interactions, factorial designs have maximum efficiency in estimating main effects.
2. If interaction exists, factorial designs are necessary to reveal and identify the interactions.
3. Since factor effects are measured over varying levels of other factors, conclusions apply to wide range of conclusions.
4. Maximum use is made of the data since all main effects and interactions are calculated from all of the data.
5. Factorial designs are orthogonal; all estimated effects and interactions are independent of effects of other factors. Independence, in this context, means that when we estimate a main effect, for example, the results we obtain is due only to the main effect of interest, and is not influenced by other factors in the experiment.
6. A greater precision can be obtained in estimating the overall main factor effects.
7. Additional factors can help to extend validity of conclusions derived.

Experimental Design Means:

DOE (Design of Experiments):

"DOE is a systematic series of tests, in which purposeful changes are made to input factors, so that you may identify causes for significant changes in the output responses." [67-18]

Objective of experiment design:

The main objective of experiment design is to obtain the maximum information with the minimum number of experiments.

In simple terms…

- Specify experimental objective
- Specify experimental conditions
  - Factors (number, identity)
  - Response (and method of measurement)
  - Levels (number, identity, values, method of determination)
  - Number of trials

Factorial Design Can Be Used To

- Identify factors with significant effects on the response
- Identify interactions among factors
- Identify which factors have the most important effects on the response
- Decide whether further investigation of a factor's effect is justified
- Investigate the functional dependence of a response on multiple factors simultaneously (if and only if you test many levels of each factor)

Types of Factorial Design

Factorial Designs are mainly divided into two parts.

1. Full Factorial design.
2. Fractional factorial design.

Full Factorial Design

Definition:

"A design in which every setting of every factor appears with every setting of every other factor is a full factorial design." Full factorial designs not recommended for 5 or more factors. Full factorial design is again classified depending on the no. of Levels as follows:

- Two level full factorial design.

Here, the number of levels are kept constant i.e. 2 & no. of factors are variable. (2, 3, 4….). These levels are called 'High' and 'Low' or +1 and -1, respectively. E.g. 2^2 factorial designs. (Here, no. of levels are 2 & no. of factors are 2) 2^3 factorial designs. (Here, no. of levels are 2 & no. of factors are 3) 2^4 factorial designs. (Here, no. of levels are 2 & no. of factors are 4) And so on.

- Three level full factorial design.

Here, the number of levels are kept constant i.e. 3 & no. of factors are variable. (2, 3, 4….). These levels are called 'High', 'Medium' and 'Low'. E.g. 3^2 factorial designs. (Here, no. of levels are 3 & no. of factors are 2) 3^3 factorial designs (Here, no. of levels are 3 & no. of factors are 3) 3^4 factorial designs. (Here, no. of levels are 3 & no. of factors are 4) And so on.

A common experimental design is one with all input factors set at two levels each. These levels are called `high' and `low' or `+1' and `-1', respectively. A design with all possible high/low combinations of all the input factors is called a full factorial design in two levels. If there are k factors, each at 2 levels, a full factorial design has 2^k runs. As shown by the above table, when the number of factors is 5 or greater, a full factorial design requires a large number of runs and is not very efficient. Therefore, a fractional factorial design or a Plackett-Burman design is a better choice for 5 or more factors.

Fractional factorial designs

Definition

"A factorial experiment in which only an adequately chosen fraction of the treatment combinations required for the complete factorial experiment is selected to be run." Even if the number of factors, k, in a design is small, the 2^k runs specified for a full factorial can quickly become very large. For example, 2^6 = 64 runs are for a two-level, full factorial design with six factors. To this design we need to add a good number of center point runs and we can thus quickly run up a very large resource requirement for runs with only a modest number of factors. The solution to this problem is to use only a fraction of the runs specified by the full factorial design. This runs to make and which to leave out is the subject of interest here. In general, we pick a fraction such as ½, ¼, etc. of the runs called for by the full factorial. We use various strategies that ensure an appropriate choice of runs. Properly chosen fractional factorial designs for 2-level experiments have the desirable properties of being both balanced and orthogonal.

Use of fractional factorial designs

1. The basic purpose of a fractional factorial design is to economically investigate cause-and-effect relationships of significance in a given experimental setting. Because, we are able to choose fractions of a full design, and hence be more economical.
2. With designs of resolution three, and sometimes four, we seek to screen out the few important main effects from the many less important others. For this reason, these designs are often termed main effects designs, or screening designs.
3. Designs of resolution five, and higher, are used for focusing on more than just main effects in an experimental situation. These designs allow us to estimate interaction effects and such designs are easily augmented to complete a second-order design.
4. There are a number of functional purposes for which designs are designed to troubleshoot a process, to determine bottlenecks, or to specify which component(s) of a product are most in need of improvement.

Experiments might also be designed to optimize yield, or to minimize defect levels, or to move a process away from an unstable operating zone. All these aims and purposes can be achieved using fractional factorial designs and their appropriate design enhancements.

Applications of Factorial Designs

1. To Optimize Animal Experiments and Reduce Animal Use:
2. Development and Characterization of Insecticidal Soap from Neem oil:
3. The use of nonregular fractional factorial designs in combination toxicity studies:
4. Simultaneous effects of nutritional and environmental factors on growth and flesh quality of Perca fluviatilis using a fractional factorial design study:
5. To Study and assess the single and combined benefits of Drug interventions in a Controlled clinical Trial.

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Fig. 1: Pharmaceutical applications of solid dispersion:[5,6,7]

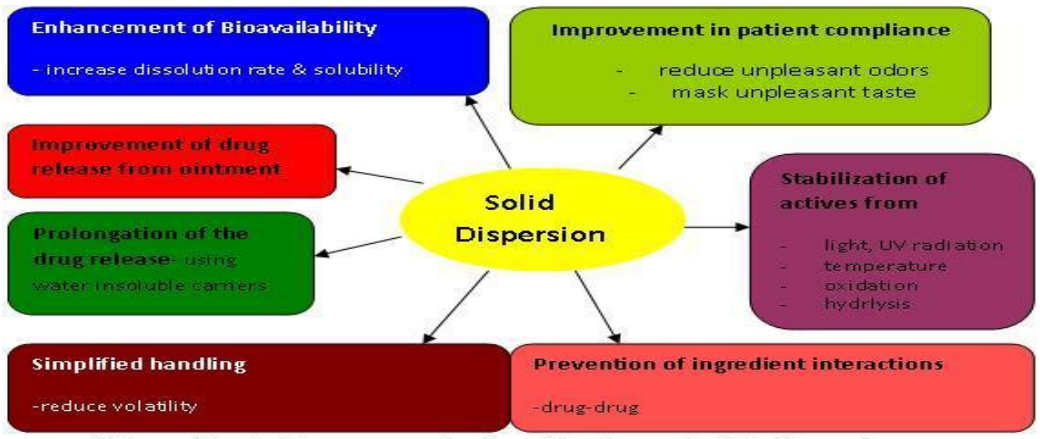

Figure No. 1: Pharmaceutical applications of solid dispersion.

Fig. 2: Elements of Experimental Design.

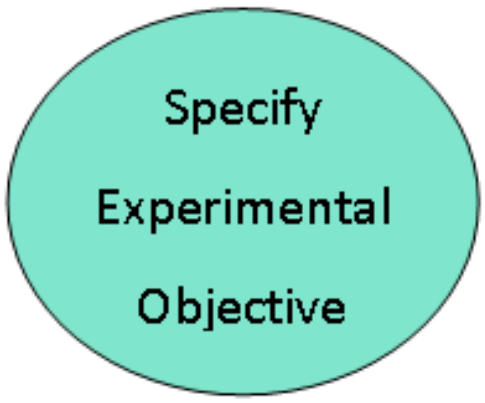

Table 1: Materials used as carrier for solid dispersion.

SR. No.	**Sugars**	**Dextrose, sucrose, galactose, sorbitol, maltose, xylitol mannitol ,lactose**
1.	Acids	Citric acid, succinic acid
2.	Polymeric materials	Povidone (PVP), polyethylene glycol (PEG), hydroxypropyl methyl cellulose, methyl cellulose, hydroxy ethyl cellulose, cyclodextrin, hydroxy propyl cellulose, pectin, galactomannan.
3.	Insoluble or enteric polymer	Hydroxy propyl methyl cellulose phthalate, eudragit L100, eudragit S100, Eudragit RL, Eudragit RS.
4.	Surfactants	Polyoxyethylene stearate, renex, poloxamer 188, texafor AIP, deoxycholic acid, tweens, spans.
5.	Miscellaneous	Pentaerythritol, pentaerythrityl tetraacetate, urea, urethane, hydroxy alkyl xanthins

Table 2: Number of Runs for a 2^k Full Factorial.

Number of Factors	**Number of Runs**
2	4
3	8
4	16
5	32
6	64
7	128

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