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Solid dispersion technique for improving solubility of some poorly soluble drugs

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ABSTRACT

Solid dispersion is one of these methods, which was most widely and successfully applied to improve the solubility, dissolution rates and consequently the bioavailability of poorly soluble drugs. The solid dispersion is based on the concept that the drug is dispersed in an inert water-soluble carrier at solid state. Several water soluble carriers such as methyl cellulose, urea, lactose, citric acid, polyvinyl pyrrolidone and polyethylene glycols 4000 and 6000 are used as carriers for solid dispersion. Thus the solid dispersion technique can be successfully used for the improvement of dissolution of Paracetamol. Polyvinyl pyrrolidone has been used for the preparation of solid dispersion as a component of the binary system for various drugs such as Tenoxicam.

Keywords*:* Solid dispersion, Polyvinyl pyrrolidone, Paracetamol, Tenoxicam.

INTRODUCTION

Solid Dispersions:
The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles[1].

Oral bioavailability of a drug depends on its solubility and/or dissolution rate, therefore efforts to increase dissolution of drugs with limited water solubility is often needed. Improvement in the dissolution rate of the poorly soluble drugs after oral administration is one of the most crucial challenges in modern pharmaceutics. Many methods are available to improve these characteristics including salt formation, micronization and addition of solvent or surface-active agents. In this study polyethylene glycol was selected and solid dispersion was prepared by the method of solvent evaporation [2].

Paracetamol is a potent anti-inflammatory analgesic agent indicated for acute and chronic treatment of rheumatoid arthritis, osteoarthritis, and ankylosing spondylytis. Paracetamol suffered from low and variable bioavailability which was attributed to its low water solubility. Several ways have been used to improve the oral bioavailability of poorly soluble drugs as an example solid dispersion technique with water soluble carriers. The increase in dissolution rate of poorly water soluble drugs from SDs can be attributed to one or combination of different factors Among the popular carriers used in the formulation of SD are polyethyleneglycols (PEGs). They are widely used because of their hydrophilicity, low melting point, and low toxicity. The development of a pharmaceutical

formulation is usually a trial and error technique including a careful control of the variables one at a time in a series of logical steps. This is generally a time consuming method in which the effect of each experimental variable will be investigated separately, while keeping all others constant [3]. Besides, variables may interact with each other and the magnitude of the effect caused by altering one factor will depend on the magnitude of one or more other factors. Such interactions cannot be elucidated by classical methods. The use of factorial design experiment is an efficient method of indicating the relative significance of a number of variables in the production of a given result. In addition it offers the advantage to provide a way of analyzing the results to decide on most significant variables. However, the most attractive option for increasing the release rate is improvement of the solubility through formulation approaches. Although salt formation, solubilization and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs 2-4 there are practical limitation of these techniques. In 1961, Sekiguchi and Obi 5 developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water soluble drugs can be overcome. This method, which was later, termed solid dispersion which involved the formation of eutectic mixture of drugs with water-soluble carriers by the melting of their physical mixtures[2].

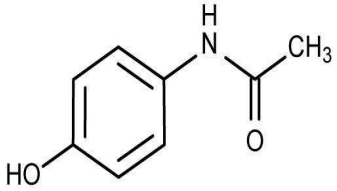
Objective of this study is
1. To acquire knowledge of solid dispersion.
2. To study the preparation, evaluation, literature of solid dispersion.
3. To study different methods of solid dispersion.
4. To study the evolution parameter of solid dispersion.

MATERIALS AND METHODS

Paracetamol, PEG 4000&6000, Methyl cellulose, Sodium Hydroxide, Potassium dihydrogen phosphate, distilled water.

Drug: Paracetamol
Monograph of Paracetamol

Acetaminophen



$C_8H_9NO_2$ **Molecular Weight: 151.16**
Paracetamol is 4-hydroxyacetanilide.

Category: Analgesic, Antipyretic.

Dose: 500mg to 0.1g every 4 to 6 hrs, up to 4gm daily in divided doses.

Description: White crystals or white, crystalline powder.

Solubility: freely soluble in ethanol (95%) & in acetone; sparingly soluble in water; very slightly in dichloromethane & in ether.

Storage: Store in well-closed, light-resistant containers.

STANDARDS: Paracetamol contains not less than 90% & not more than 101.0% of C8H9NO2. Calculated with reference to the dried substance.

Identification Test A may be omitted if tests B , C , D & E are carried out. Test B, C & D may be omitted if tests A & E are carried out.

A: The infra-red absorption spectrum, Appendix 5.4, is concordant with reference spectrum of paracetamol or with the spectrum obtained from paracetamol RS.

B: Dissolve 50mg in sufficient methanol to produce 100ml. To 1ml of this solution add 0.5 ml of 0.1 M Hydrochloric acid & dilute to 100ml with methanol. Protect the resulting solution from bright light and immediately measure the absorbance at the maximum at about 249 nm. Absorbance at about 249 nm, about 0.44, Appendix 5.5.

C: Boil 0.1 gm in 1ml of Hydrochloric acid for 3 minutes, add 10ml of water & cool; no precipitate is produced. Add 0.05 ml of 0.0167 M potassium dichromate; a violet colour develops which does not turn red.

D: Gives the reaction of acetyl groups, Appendix 3.1.

E: melts between 168^0 & 172^0 , Appendix 8.8
Heavy metals: Not more than 10 ppm, determined on 2.0g by method C, Appendix 3.12.

4-Aminophenol: Dissolve 0.50 gm in sufficient methanol (50%) to produce 10ml. Add 0.2 ml of freshly prepared alkaline sodium nitroprusside solution, mix & allow to stand for 30 minutes .Any Blue colour in the solution is not more intense than that in 10ml of solution prepared at the same manner containing 0.5gm of 4-aminophenol- free paracetamol & 0.5 ml of 0.005% w/v solution of 4- aminophenol in methanol (50%) (50ppm).

Related substances: Carry out the method for thin layer chromatography. Appendix 4.6 , using silica gel GF 254 as the coating substances & a mixture of 65 volumes of chloroform , 25 volumes of acetone & 10 volumes of toluene as the mobile phase but allowing the solvent front to a sends 14 cm above the line of application. Apply separately to the plate 200ul of solution (1) & 40ul of each solution (2), (3) & (4). for solution (1) transfer 1.0g of the substance being examined , finely powdered , to a ground – glass stoppered 15ml centrifuge tube , add 5ml of peroxide –free ether , shake mechanically for 30 minutes & centrifuge at 1000rpm for 15 minutes or until a clear supernatant liquid is obtained . For solution (2) dilute 1ml of solution (1) to 10 ml with ethanol (95%) solution (3) contains 0.005% w/v of 4-chloroacetanilide in ethanol (95%). For solution (4) dissolve 0.25 gm of 4-chloroacetanilide & 0.1g of the substance being examined in sufficient ethanol (95%) to produce 100 ml. After removal of the plate, dry it in a current of warm air & examine under ultra-violet light (254nm). Any spot corresponding to 4-chloroacetanilide in the chromatogram obtained with solution (3). Any other secondary spot in the chromatogram obtained with solution (2) is not more intense than the spot in the chromatogram obtained with solution (3). The chromatogram obtained with solution (4) shows two clearly separated spots, the spot corresponding to paracetamol having the lower Rf value.

Sulphated Ash: Not more than 0.1 %, Appendix 3.22.

Loss on drying: Not more than 0.5 % determined on 1g by drying in an oven at 105^0, Appendix 8.6.

Assay: Weigh accurately about 0.5 g , dissolve in a mixture of 10 ml water & 50 ml of 1 M sulphuric acid . Boil under reflux condenser for 1 hour, cool & dilute to 100 ml with water. To 2oml of the solution add 40 ml of water , 40g of water in the form of ice , 15 ml of 2 M hydrochloric acid & 0.1 ml of ferroin solution & titrate with 0.1 M cerric ammonium sulphate until a yellow colour is produced . Perform a blank of determination & make any necessary correction. Each ml of 0.1 M cerric ammonium sulphate is equivalent to 0.00756 gm of $C_8H_9NO_2$ [30].

Monograph of PEG4000
Macrogol 4000
Polyethylene Glycol 4000 is a mixture of the polycondensation products of ethylene oxide and water obtained under controlled conditions. It is represented by the formula $HOCH_2[CH_2OCH_2]nCH_2OH$, where n is between 69and 84.

Description: A creamy white , hard , wax-like solid, powder or flakes; odour, faint and characteristic.

Tests :
Appearance of solution (2.4.1).A 20.0percent w/v solution is not more than reference solution BYS6.

pH(2.4.24).4.5 to 7.5, determined in 5.0 percent w/v solution.

Freezing point (2.4.11). $53^0$to $56^{0.}$

Hydroxyl value (2.3.27). 30 to 36, determined on 20.0g

Viscosity (2.4.28). 76mm^2s^{-1}, determined at 100^0 by method A using a U- tube viscometer (size E).

Arsenic (2.3.10). Mix 3.3 g with 3 g of anhydrous sodium carbonate, add 10ml of bromine solution and mix thoroughly. Evaporate to dryness on a water-bath, gently ignite and dissolve the cooled residue in 16 ml of brominated hydrochloric acid and 45 ml of water. Remove the excess of bromine with 2 ml of stannous chloride solution AsT. The resulting solution complies with the limit test for arsenic (3ppm).

Heavy metals (2.3.13). Dissolve 4.0 g in 5 ml of a 1.0 percent w/v solution of hydrochloric acid and sufficient water to produce 25 ml. The solution complies with the limit test for heavy metals, Method A (5ppm).

Sulphated ash(2.318). Not more than 0.1 percent.

Storage. Store protected from moisture[31] .

Monograhh of PEG6000
Macrogol 6000

Polyethylene Glycol 6000 is a mixture of the polycondensation products of ethylene oxide and water obtained under controlled conditions. It is represented by the formula $HOCH_2[CH_2OCH_2]nCH_2OH$, where n is between 112and 158.
Description: A creamy white, wax-like solid, powder or flakes; odour, faint and characteristic.

Tests
Appearance of solution (2.4.1): A 15.0percent w/v solution is not more intensely coloured than reference solution BYS6.

pH(2.4.24).4.5 to 7.5: determined in 5.0 percent w/v solution.

Freezing point (2.4.11): $53^0$to $56^{0.}$

Viscosity (2.4.28): 250mm^2s^{-1} to 390 mm^2s^{-1}, determined at 100^0 by method A using a U- tube viscometer (size E).

Arsenic (2.3.10): Mix 3.3 g with 3 g of anhydrous sodium carbonate, add 10ml of bromine solution and mix thoroughly. Evaporate to dryness on a water-bath, gently ignite and dissolve the cooled residue in 16 ml of brominated hydrochloric acid and 45 ml of water. Remove the excess of bromine with 2 ml of stannous chloride solution AsT. The resulting solution complies with the limit test for arsenic (3ppm).

Heavy metals (2.3.13): Dissolve 4.0 g in 5 ml of a 1.0 percent w/v solution of hydrochloric acid and sufficient water to produce 25 ml. The resulting solution complies with the limit test for heavy metals, Method A (5ppm).

Sulphated ash(2.318). Not more than 0.1 percent.

Storage: Store protected from moisture [31].

Monograph of Methyl cellulose
Cellulose Methyl Ether

Methylcellulose is a cellulose having some of the hydroxyl groups in the form of the methyl ether. Various grades are available and are distinguished by a number indicative of the apparent viscosity in millipascal seconds of a 2% w/w solution measured at 20^o.

Category: Bulk laxative; pharmaceutical aid (tablet excipient; suspending agent).

Description: White or yellowish white or greyish white powder or granules; practically odourless; hygroscopic after drying.

Solubility: Practically insoluble in hot *water*, in *acetone*, in *ethanol*, in *ether* and in *toluene*. It dissolves in cold *water* forming a colloidal solution.

Storage: Store in well-closed containers.

Labelling: The label states the apparent viscosity in millipascal seconds of a 2% w/w solution.

STANDARDS
Methylcellulose contains not less than 27.5 per cent and not more than 31.5 per cent of methoxyl ($-OCH_3$) groups, calculated with reference to the dried substance.

Identification; pH; Heavy metals; Chloride: Complies with the requirements stated under Hydroxypropylcellulose.

Clarity and colour of solution: Whilst stirring, introduce a quantity equivalent to 1.0 g of the dried substance into 50 g of *carbon dioxide-free water* heated to 90°. Allow to cool, dilute to 100 g with the same solvent and continue stirring until solution is complete. Allow to stand at 2° to 8° for 1 hour. The resulting solution is not more opalescent than *opalescence standard OS3*, ***Appendix 6.1***, and is not more intensely coloured than *reference solution YS6*, ***Appendix 6.2***.

Apparent viscosity: Not less than 75% and not more than 140% of the declared value, determined by the following method. To 150 g of *water* heated to 90° add, with stirring, a quantity equivalent to 6 g of the dried substance. Stir with a propeller-type stirrer for 10 minutes, place the flask in a bath of iced *water*, continue the stirring and allow to remain in the bath of *iced* water for 40 minutes to ensure that solution is complete. Adjust the weight of the solution to 300 g and centrifuge the solution to expel any trapped air. Determine the viscosity at 20° by *Method C*, ***Appendix 8.14***, using a shear rate of 10 s^{-1}.

Sulphated ash: Not more than 1.0%, ***Appendix 3.22***.

Loss on drying: Not more than 5.0%, determined on 1 g by drying in an oven at 105°, ***Appendix 8.6***.

Assay: Weigh accurately about 50 mg in a *hard gelatin capsule shell*, place the capsule and the contents in a 50-ml boiling flask and carry out the *determination of methoxyl*, ***Appendix 3.19***. Each ml of *0.1M sodium thiosulphate* is equivalent to 0.0005172 g of methoxyl ($-OCH_3$) groups[30].

Method of preparation of solid dispersion
Solvent melting method:
Accurately weighed drug is dissolved in organic solvent. The solution is incorporated into the melt of polyethylene glycol and cooled suddenly and mass is kept in desiccators for complete drying. The solidified mass is crushed, pulverized and passed through sieve . 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 (less than 50 mg).

Material :
Paracetamol, PEG 4000 PEG 6000, Potassium dihydrogen phosphate Sodium hydroxide, distilled water.

Drug: Paracetamol

Preparation of solid dispersion of paracetamol
Solid dispersions were prepared by melting the accurately weighed amounts of carriers (PEG 4000, PEG 6000 and Methyl cellulose) in a water bath and the drug was dispersed in the molten solution. Solvent Evaporation method was used for the preparation of solid dispersions. Briefly appropriate amount of paracetamol was taken in china dish and required amount of carriers (PEG 4000, PEG 6000 and Methyl cellulose) were added to prepare required drug to

carrier ratio for formulations .Then the mixture was heated under controlled temperature to melt drug and carrier with continuous stirring. The melted preparation was transferred to porcelain tile to solidify and cooled in an ice bath. The solid dispersions prepared were pulverized and sifted (80#) and stored in a desiccators.

Table 1: Drug: Carrier formulation ratio

Formulation Code	Carrier	Drug: carrier ratio
SD1	PEG 4000	1:1
SD2		1:2
SD3		1:3
SD4		1:4
SD5	PEG 6000	1:1
SD6		1:2
SD7		1:3
SD8		1:4
SD9	Methyl cellulose	1:1
SD10		1:2
SD11		1:3
SD12		1:4

Methods of Preparation of Solid Dispersions:

1. Melting method

The melting or fusion method, first proposed by (Sekiguchi and Obi 1961) 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. 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[7].

2. Solvent method:

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. The first step in the solvent method is the preparation of a solution containing both matrix material and drug. The second step involves the removal of solvent(s) resulting in formation of a solid dispersion. Mixing at the molecular level is preferred, because this leads to optimal dissolution properties[6].

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
4) The selection of a common volatile solvent.
5) The difficulty of reproducing crystal form[5].

3. Melting solvent method (melt evaporation):

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[6]. 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[7]. 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[9].

4. Melt extrusion method:

The drug/carrier mix is typically processed with a twin-screw extruder. The drug/carrier mix is simultaneously melted, homogenized and then extruded and shaped as tablets, granules, pellets, sheets, sticks or powder. The intermediates can then be further processed into conventional tablets. An important advantage of the hot melt extrusion method is that the drug/carrier mix is only subjected to an elevated temperature for about 1 min, which enables drugs that are somewhat thermo labile to be processed[10].

5. Lyophilisation Technique:

Freeze-drying involves transfer of heat and mass to and from the product under preparation. This technique was proposed as an alternative technique to solvent evaporation. Lyophilisation has been thought of a molecular mixing technique where the drug and carrier are co dissolved in a common solvent, frozen and sublimed to obtain a lyophilized molecular dispersion.(Betageri GV et al).An important advantage of freeze drying is that the drug is subjected to minimal thermal stress during the formation of the solid dispersion. However, the most important advantage of freeze drying is that the risk of phase separation is minimized as soon as the solution is vitrified. An even more promising drying technique is spray-freeze drying. The solvent is sprayed into liquid nitrogen or cold dry air and the frozen droplets are subsequently lyophilized. The large surface area and direct contact with the cooling agent result in even faster vitrification, thereby decreasing the risk for phase separation to a minimum .Moreover, spray freeze drying offers the potential to customize the size of the particle to make them suitable for further processing or applications like pulmonary or nasal administration[9].

6. Melt Agglomeration Process:

This technique has been used to prepare SD wherein the binder acts as a carrier. In addition, SD(s) are prepared either by heating binder, drug and excipient to a temperature above the melting point of the binder (melt- in procedure) or by spraying a dispersion of drug in molten binder on the heated excipient (spray-on procedure) by using a high shear mixer. A rotary processor has been shown to be alternative equipment for melt agglomeration. The rotary processor might be preferable to the high melt agglomeration because it is easier to control the temperature and because a higher binder content can be incorporated in the agglomerates. The effect of binder type, method of manufacturing and particle size are critical parameters in preparation of SD(s) by melt agglomeration. Since these parameters result in variations in dissolution rates, mechanism of agglomerate formation and growth, agglomerate size, agglomerate size distribution and densification of agglomerates. It has been investigated that the melt in procedure gives a higher dissolution rates than the spray-on procedure with PEG 3000, poloxamer 188 and gelucire 50/13 attributed to immersion mechanism of agglomerate formation and growth. In addition the melt in procedure also results in homogenous distribution of drug in agglomerate. Larger particles results in densification of agglomerates while fine particle cause complete adhesion to the mass to bowl shortly after melting attributed to distribution and coalescence of the fine particles[10].

7. The use of surfactant:

The utility of the surfactant systems in solubilization is well known. Adsorption of surfactant on solid surface can modify their hydrophobisity, surface charge, and other key properties that govern interfacial processes such as flocculation/dispersion, floatation, wetting, solubilization, detergency, enhanced oil recovery and corrosion inhibition. Surfactants have also been reported to cause solvation/plasticization, manifesting in reduction of melting the active pharmaceutical ingredients, glass transition temperature and the combined glass transition temperature of solid dispersions. Because of these unique properties, surfactants have attracted the attention of investigators for preparation of solid dispersions.

8. Electrospinning:

Electrospinning is a process in which solid fibers are produced from a polymeric fluid stream solution or melt delivered through a millimeter-scale nozzle. This process involves the application of a strong electrostatic field over a conductive capillary attaching to a reservoir containing a polymer solution or melt and a conductive collection screen. Upon increasing the electrostatic field strength up to but not exceeding a critical value, charge species accumulated on the surface of a pendant drop destabilize the hemispherical shape into a conical shape (commonly known as Taylor s cone)[11]. Beyond the critical value, a charged polymer jet is ejected from the apex of the cone (as a way of relieving the charge built-up on the surface of the pendant drop). The ejected charged jet is then carried to

the collection screen via the electrostatic force. The Coulombic repulsion force is responsible for the thinning of the charged jet during its trajectory to the collection screen. The thinning down of the charged jet is limited by the viscosity increase, as the charged jet is dried . This technique has tremendous potential for the preparation of nanofibres and controlling the release of biomedicine, as it is simplest, the cheapest this technique can be utilized for the preparation of solid dispersions in future[12].

9. Super Critical Fluid (Scf) Technology:

Supercritical fluid methods are mostly applied with carbon dioxide (CO2), which is used as either a solvent for drug and matrix or as an anti-solvent[13]. When supercritical CO2 is used as solvent, matrix and drug are dissolved and sprayed through a nozzle, into an expansion vessel with lower pressure and particles are immediately formed. The adiabatic expansion of the mixture results in rapid cooling. This technique does not require the use of organic solvents and since CO2 is considered environmentally friendly, this technique is referred to as 'solvent free'. The technique is known as Rapid Expansion of Supercritical Solution (RESS). However, the application of this technique is very limited, because the solubility in CO2 of most pharmaceutical compounds is very low (<0.01wt-%) and decreases with increasing polarity. Therefore, scaling up this process to kilogram-scale will be impractical[14].

10. Direct capsule filling :

Direct filling of hard gelatin capsules with the liquid melt of solid dispersions avoids grinding-induced changes in the crystallinity of the drug . This molten dispersion forms a solid plug inside the capsule on cooling to room temperature, reducing cross contamination and operator exposure in a dust-free environment, better fill weight and content uniformity was obtained than with the powder-fill technique. However, PEG was not a suitable carrier for the direct capsule-filling method as the water-soluble carrier dissolved more rapidly than the drug, resulting in drug-rich layers formed over the surface of dissolving plugs, which prevented further dissolution of the drug[15,16].

11. Dropping solution method:

The dropping method facilitate the crystallization of different chemicals and produces round particles from melted solid dispersions. In laboratory-scale preparation, a solid dispersion of a melted drug-carrier mixture is pipetted and then dropped onto a plate, where it solidifies into round particles. The size and shape of the particles can be influenced by factors such as the viscosity of the melt and the size of the pipette. Because viscosity is highly temperature-dependent, it is very important to adjust the temperature so that when the melt is dropped onto the plate it solidifies to a spherical shape[17].

The use of carriers that solidify at room temperature may aid the dropping process. The dropping method not only simplifies the manufacturing process, but also gives a higher dissolution rate. It does not use organic solvents and, therefore, has none of the problems associated with solvent evaporation. The method also avoids the pulverization, sifting and compressibility difficulties encountered with the other melt methods. Disadvantages of the dropping method are that only thermo stable drugs can be used and the physical instability of solid dispersions is a further challenge.

12. Co-precipitation method:

Co-precipitation is a recognized technique for increasing the dissolution of poorly water soluble drugs, so as to consequently improve bioavailability. In this method nonsolvent is added drop wise to the drug and carrier solution, under constant stirring. In the course of the nonsolvent addition, the drug and carrier are co-precipitated to form micro particles. At the end, the resulted micro particle suspension is filtered and dried40. The required quantity of polymer and the drug were mixed and then solvent was added to obtain clear solution. The Solution was first dried under vacuum at room temperature and kept inside incubator (370c) for 12 hrs. Finally it was passed through sieves41[18].

ADVANTAGES OF SOLID DISPERSIONS:

Generally, solid dispersion is mainly used

1. To reduced particle size.
2. To improve wettability.
3. To improve porosity of drug.
4. To decrease the crystalline structure of drug in to amorphous form.
5. To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical.

6. To mask the taste of the drug substance.
7. To prepare rapid disintegration oral tablets.
8. To obtain a homogenous distribution of small amount of drugs at solid state.
9. To stabilize unstable drugs.
10. To dispense liquid or gaseous compounds.
11. To formulate a faster release priming dose in a sustained release dosage form.
12. To formulate sustained release dosage or prolonged release regimens of soluble drugs using poorly soluble or insoluble carriers.

1. Particles with reduced particle size

Molecular dispersions, as solid dispersions, represent the last state on particle size reduction, and after carrier dissolution the drug is molecularly dispersed in the dissolution medium. Solid dispersions apply this principle to drug release by creating a mixture of a poorly water soluble drug and highly soluble carriers[20]. A high surface area is formed, resulting in an increased dissolution rate and, consequently, improved bioavailability[20].

2. Particles with improved wettability

A strong contribution to the enhancement of drug solubility is related to the drug wettability improvement verified in solid dispersions[22]. It was observed that even carriers without any surface activity, such as urea improved drug wettability. Carriers with surface activity, such as cholic acid and bile salts. When used, can significantly increase the wettability property of drug. Moreover, carriers can influence the drug dissolution profile by direct dissolution or co-solvent effects[21].

3. Particles with higher porosity

Particles in solid dispersions have been found to have a higher degree of porosity[23]. The increase in porosity also depends on the carrier properties; for instance, solid dispersions containing linear polymers produce larger and more porous particles than those containing reticular polymers and, therefore, result in a higher dissolution rate[24]. The increased porosity of solid dispersion particles also hastens the drug release profile.

4. Drugs in amorphous state

Poorly water soluble crystalline drugs, when in the amorphous state tend to have higher solubility[25]. The enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process[26]. In solid dispersions, drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form[20]. For drugs with low crystal energy (low melting temperature or heat of fusion), the amorphous composition is primarily dictated by the difference in melting temperature between drug and carrier. For drugs with high crystal energy, higher amorphous compositions can be obtained by choosing carriers, which exhibit specific interactions with them[26].

5. Rapid disintegration of oral tablets

Drug is formulated with hydrophilic carrier (e.g. PEG) as a solid dispersion to increase its aqueous solubility and dissolution. Then superdisintegrant (e.g. croscarmellose sodium) is used in tablet formulation to achieve rapid disintegration of tablets prepared by wet granulation method. These rapidly disintegrating tablets can be used as an alternative to parenteral therapy enabling patient for self-medication even without the aid of water.

DISADVANTAGES OF SOLID DISPERSIONS:

Serajuddin (1999) identified some problems limiting the commercial application of solid dispersion which involved (a) its method of preparation, (b) reproducibility of its physicochemical properties, (c) its formulation into dosage forms, (d) the scale up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle. Solid dispersions are not broadly used in commercial products due to mainly the problem of crystallization of the components from amorphous state during processing (mechanical stress) or storage (temperature and humidity stress). Moisture may increase drug mobility and promote drug crystallization and thus may hamper storage stability of amorphous pharmaceuticals .Phase separation, crystal growth or conversion of a product to more stable structure from metastable crystalline form during storage are also considered to be major hurdles to commercialize solid dispersions as they result in decreased solubility and thus dissolution rate[27].

Evaluation of Solid dispersions:

1. Physical characterization and saturation solubility study

The excess amount of the formulations (PMs and SDs) was added to conical flask Containing 10 ml of distilled water and subjected to shaking on a rotary shaker for 48 hours at 37°C. Then the flasks were removed and filtered. Suitable aliquots were Withdrawn from the filtered solution and analyzed for the drug content after appropriate dilution with distilled water and compared with pure drug solubility.

2. Drug content analysis

Preparations equivalent to 20 mg was weighed accurately and transferred to 100 ml volumetric flask and dissolved in phosphate buffer pH 5.8. The volume was made up with phosphate buffer pH 5.8 up to the mark. After suitable dilution, the absorbance of the above solution was measured at 243 nm using appropriate blank solution. The drug content of paracetamol was calculated using calibration curve.

***3. In vitro* release studies**

Accurately weighed amount of sample was taken for dissolution studies. Aliquots of sample were withdrawn at predetermined intervals of time and analyzed for drug release by measuring the absorbance at 243nm using phosphate buffer pH 5.8 as dissolution medium. The volume withdrawn at each time intervals were replaced with same quantity of fresh medium[28].

Calibration Curve by UV Spectrophotometry

Preparation of standard curve of paracetamol:

For the calibration, stock solution of paracetamol was prepared at 30 µg/mL in phosphate buffer saline (pH 7.4). The linearity of the calibration curve (Coefficient of Determination R^2 = 0.99) was obtained in a concentration range from 2 µg/mL to 14 µg/mL by Unicam UV-Visible Spectrophotometer at 240 nm as shown in figure 3.10.

Table no.2 Absorbance of paracetamol in phosphate buffer saline at 240 nm by UV.

Concentration (µg/ml)	Absorbance
2.5	0.180
5	0.301
7.5	0.524
10	0.720
12.5	0.910

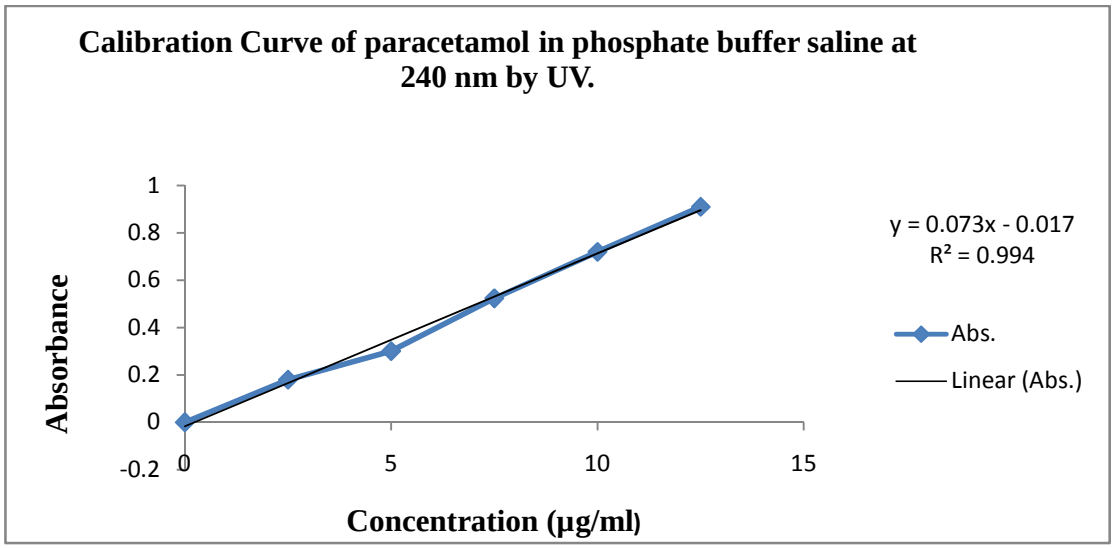


Figure No 1. Calibration curve of paracetamol in phosphate buffer saline at 240 nm by UV.

In vitro dissolution data for pure drug and solid dispersions

Table No:2 Diffusion profile of Paracetamol: PEG 6000 formulation in phosphate buffer pH 5.8

Time in minute	Cumulative Drug Release%				
	Pure drug	1:1	1:2	1:3	1:4
15	23.91	31.31	35.93	40.62	59.11
30	25.02	32.6	36.92	42.1	61.7
60	27.3	33.47	38.21	45.8	69.65

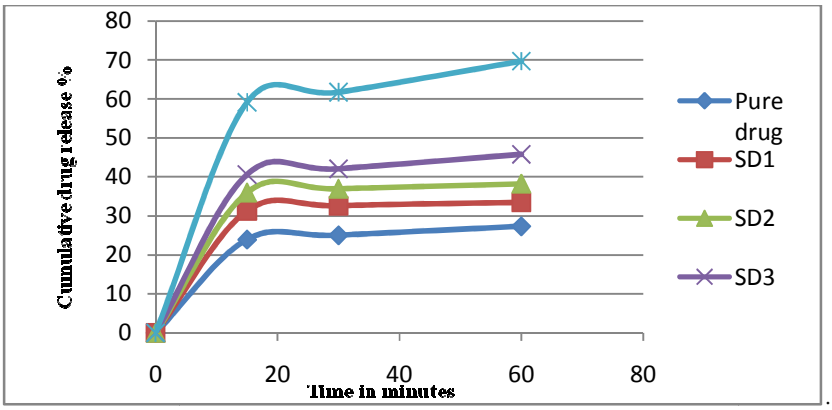


Figure No. 2: Diffusion profile of Paracetamol: PEG 6000 formulation in phosphate buffer pH 5.8

Table No.3 Diffusion profile of Paracetamol: PEG 4000 formulation in phosphate buffer pH 5.8

Time in minute	Cumulative Drug Release%				
	Pure drug	1:1	1:2	1:3	1:4
15	23.91	30.80	35.75	38.58	47.65
30	25.02	34.52	36.55	40.13	55.60
60	27.3	35.07	37.54	40.93	60.59

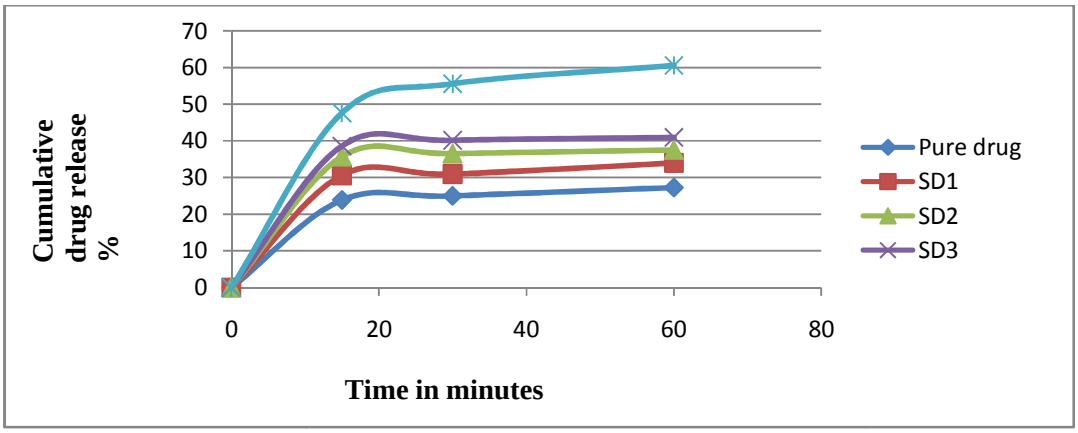


Figure No. 3 : Diffusion profile of Paracetamol: PEG 4000 formulation in phosphate buffer pH 5.

Table No.4 Diffusion profile of Paracetamol: Methyl Cellulose formulation in phosphate buffer pH 5.8

Time in minute	Cumulative Drug Release%				
	Pure drug	1:1	1:2	1:3	1:4
15	23.91	30.63	35.19	39.32	45.18
30	25.02	30.94	36.24	41.05	50.60
60	27.3	33.96	37.41	42.41	63.61

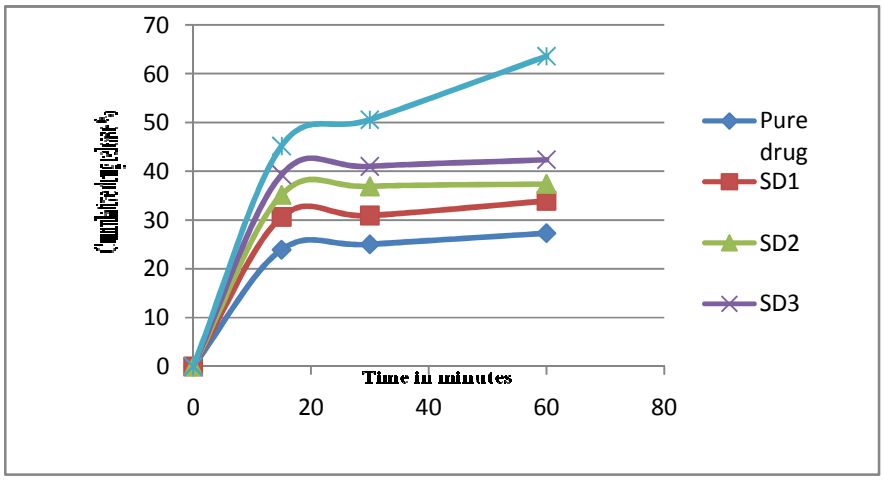


Figure No. 4: Diffusion profile of Paracetamol: Methyl Cellulose formulation in phosphate buffer pH 5.8

RESULTS AND DISCUSSION

Drug content analysis

Drug content is found to be between 60.59 % and 69.65 %. All the SDs showed presence of high drug content and low standard deviations of results. It is indicated that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for the preparation of SDs.

***In vitro* dissolution study**

The formulation of solid dispersion of paracetamol with various carriers like PEG 4000, PEG 6000 and Methyl Cellulose were screened for the selection of suitable carriers. These carriers were found to be encouraging since they did not undergo any chemical change during the preparation of solid dispersion. The solid dispersion of paracetamol with carriers PEG 4000, PEG 6000, and Methyl Cellulose showed a marked increase in the dissolution rate in pH 5.8 phosphate buffer. Dissolution of the paracetamol increased with increasing proportions of carriers and T**50%** and T**70%** values were least with the SDs of Methyl Cellulose (i.e.1:1-1:4). Above all the formulations the ratio of paracetamol: PEG 6000 (SD4) showed (1:4) maximum proving that higher concentration of matrix formed with PEG 6000 of ratio 1:4 increased the dissolution rate. These observations indicate the enhanced dissolution of SDs with increase in the concentration of carriers possibly due to the increased wettability of the drug by the carrier, drug particle size reduction in the course of the solid dispersion preparation, polymorphic transformation of drug crystals and chemical interactions between drug and carrier.

CONCLUSION

From the present study it can be easily demonstrated that, PEG 4000, PEG 6000, and Methyl Cellulose has immense potential to improve solubility characters of any less soluble or poorly soluble drug. This work also illustrates the fact that PEG 4000, PEG 6000, and Methyl Cellulose has characteristics to form molecular dispersions with the drug molecules, thereby, increasing the dissolution rate of drug and decreasing the time of release of drug from the formulated mixture.

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