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Research Article

**FORMULATION AND *INVITRO* EVALUATION OF
TOLTERIDONE TARTARATE SOLID DISPERSIONS
USING DIFFERENT POLYMERS****Sai Lakshmi Jyothirmai. Kala*, Sireesha .Challa, Gowthami. Baina Boina**

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Abstract:

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion but it is problematic if the drug is poorly soluble or poor membrane penetrability. Although salt formation, solubilization, particle size reduction have commonly used to increase dissolution rate and thereby oral absorption and bioavailability of low water soluble drugs there is practical limitation to these techniques. Among numerous ways of enhancing drug dissolution solid dispersion of drug in a water soluble polymer is one of the promising technique. Solid dispersion (SD) is defined as the dispersion of one or more active ingredients in inert carriers at solid state prepared by fusion, solvent or solvent fusion methods. The study was aimed to formulate solid dispersion tablet of Terbinafine Hydrochloride by using carriers polyethylene glycol 6000 (by melting method) and maltodextrin, urea in the drug carrier ratio of 1:1, 1:2 and 1:3. The prepared solid dispersions were characterized for their drug content, thermal studies, infrared spectral studies, aqueous solubility studies and %yield. From the results, it was clear that solid dispersion formulation showed improved dissolution rate compared to pure drug and physical mixture.

Keywords: Solid dispersion, infrared studies, tolteridone tartarate, maltodextrin, urea, PEG6000,**Corresponding author:****Sai lakshmi jyothirmai.Kala,**

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INTRODUCTION:

In order to ensure the optimum therapeutic effect of drug it is necessary to prepare the proper dosage form. To formulate an effective dosage form the drug must possess some important characteristics and one of them is the solubility in water. Since only dissolved drug can pass the gastrointestinal membrane, dissolution is one that affect the systemic absorption. Among all the routes of drug administration, oral drug delivery is the simplest and easiest way of administering drugs, because of the greater stability, smaller bulk, possess accurate dose and easy to manufacture. The oral route of drug administration is the most common and preferred method of drug delivery due to convenience and ease of ingestion. Poorly water soluble drugs having slow drug absorption leads to inadequate and variable bioavailability and gastrointestinal mucosal toxicity. This poor oral bioavailability of the drug is the major challenging task for designing the oral dosage forms. The poor oral bioavailability of the drug is due to low solubility, low dissolution of the drug rather than permeation of the drug through epithelia of gastrointestinal tract[1]. Drug absorption from the gastrointestinal tract can be limited by a number of factors; most significant contributors are poor aqueous solubility & poor membrane permeability of the drug molecule. When delivering an active agent orally, it must first dissolve in gastric and/or intestinal fluids before it can permeate the membranes of the GI tract to reach systemic circulation. Hence two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing solubility and dissolution rate of poorly water soluble drugs & enhancing permeability of poorly water-soluble drugs.

Therefore, most of the new chemical entities under development these days are intended to be used as a solid dosage form which produces an effective reproducible *in vivo* plasma concentration after oral administration. In fact, most new chemical entities are poorly soluble drugs, not well-absorbed after oral administration, which can distract from the drug's inherent efficacy.

There are various techniques available to improve the solubility of poorly soluble drugs, such as micronization, nanosuspension, modification of the crystal habits, eutectic mixtures, solid dispersions, micro emulsions, self micro emulsifying drug delivery systems, cyclodextrin inclusion and lipid based delivery systems etc[2]The most promising method for promoting dissolution is the formation of solid dispersion in a proper carrier. The conventional methods for reducing particle size include trituration, ball milling, grinding, etc.

Sekiguchi and Obi first introduced the concept of using solid dispersion to improve bioavailability of poorly water soluble drugs in 1961.

Definition of solid dispersion:-

The term solid dispersion refers to the dispersion of one or more active ingredients in an inert carriers or matrix at solid state prepared by melting, solvent evaporation or other technique of solid dispersion. Solid dispersions (SDs) have traditionally been used as an effective method to improve the dissolution properties and bioavailability of poorly water-soluble drugs. In solid dispersions systems, a drug may exist as an amorphous form in polymeric carriers, and this may result in improved solubility's and dissolution rates as compared with crystalline material. Drugs molecularly dispersed in polymeric carriers may achieve the highest levels of particle size reduction and surface area enhancement, which result in improved dissolution rates [3]

Solid dispersions are prepared to:

1. To improve drug solubility.
2. To improve drug stability.
3. To mask the bitter taste of drug.
4. To obtain required release profile

Mechanism

The basic mechanisms responsible for increasing solubility of drugs are:-

Wetting

Reduced particle size or particle agglomeration

Soluble complex formation

Advantages of Solid Dispersions:-

- ✦ Particles with reduced particle size.
- ✦ Particles with improved wettability.
- ✦ Particles with higher porosity of drug.
- ✦ Drug in amorphous form.
- ✦ To improve porosity of drug.
- ✦ To decrease the crystalline structure of drug in to amorphous form.
- ✦ To improve dissolvability in water of a poorly water-soluble drug in a pharmaceutical. [4]

Disadvantages of Solid Dispersions:-

- ✦ The major disadvantages of SDs are related to their instability.
- ✦ Several systems have shown changes in crystallinity and a decrease in dissolution rate on aging.
- ✦ By absorbing moisture, phase separation, crystal growth or a change from metastable crystalline form to stable form can take place which leads to the reduction of drug solubility.
- ✦ Moisture and temperature have more of deteriorating effect on solid dispersions than on physical mixtures. Sometimes it is difficult to handle because of tackiness [7]
- ✦ Several systems have shown changes in crystallinity and a decrease in dissolution rate on aging.
- ✦ Moisture and temperature have more of deteriorating effect on solid dispersions.

During formulation sometimes it may form hard lump which is very difficult to break on large scale.

Techniques of solid dispersion:-

- 1) Melting (Fusion) Method
- 2) Solvent Evaporation
- 3) Kneading Method
- 4) Spray Drying
- 5) Hot Melt Extrusion

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. [8]

Ex.- Albendazole and urea solid dispersion

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. [5]The film is further dried to constant weight.

Advantage:- 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.[9]

Ex.- solid dispersion sulfa thiazine and urea

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 glycol 6000 without significant loss of its solid property.

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. [5]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]

Tolterodine is an antimuscarinic drug that is used to treat urinary inconvience. Tolterodine acts on M2 and M3 subtypes of muscarinic receptors. Tolterodine are a competitive muscarinic receptor antagonist. Both urinary bladder contraction and salivation are mediated via cholinergic muscarinic receptors. After oral administration, tolterodine is metabolized in the liver, resulting in the formation of the 5-hydroxymethyl derivative, a major pharmacologically active metabolite.[8] The 5-

hydroxymethyl metabolite, which exhibits an antimuscarinic activity similar to that of tolterodine, contributes significantly to the therapeutic effect. Both tolterodine and the 5-hydroxymethyl metabolite exhibit a high specificity for muscarinic receptors, since both show negligible activity or affinity for other neurotransmitter receptors and other potential cellular targets, such as calcium channels. [11]Tolterodine has a pronounced effect on bladder function. The main effects of tolterodine are an increase in residual urine, reflecting an incomplete emptying of the bladder, and a decrease in detrusor pressure, consistent with an antimuscarinic action on the lower urinary tract. Both tolterodine and its active metabolite, 5-hydroxymethyltolterodine, act as competitive antagonists at muscarinic receptors. This antagonism results in inhibition of bladder contraction, decrease in detrusor pressure, and an incomplete emptying of the bladder.[12]

The drug is poorly soluble in water in order to increase the solubility and to enhance the oral bioavailability it is formulated in the form of solid dispersion using urea, PEG6000, pvp, urea and maltodextrin using different methods.

MATERIALS AND METHODS:

Materials:- Tolteridone tartarate was obtained as gift sample from hetero, India. Maltodextrin was procured from Himedia laboratories pvt.Ltd, Dindori, India. Polyvinyl pyrrolidone was procured from lobachemie laboratory and chemicals, Pvt. Ltd, Mumbai, India. urea was procured from universal laboratories Pvt, Ltd, Raheja centre, Mumbai, India, polyethylene glycol 6000 was procured from lobachemie reagents and fine chemicals, Mumbai, India. All chemicals and solvents used were of analytical grade.

Methods

Preparation of solid dispersion by melting method

In melting method the drug and carrier polyethylene glycol 6000 were mixed in 1:1, 1:2, and 1:3 ratios in a china dish and heated on a paraffin bath. The mixture was poured on a tile and cooled. The resulted solidified mass was dried pulverised and passed through sieve # 100.

Preparation of solid dispersion by solvent evaporation method

In solvent evaporation method, the drug and carrier polyvinyl pyrrolidone were mixed in 1:1, 1:2 and 1:3 ratios in chloroform. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100.

Preparation of solid dispersion by fusion method
Accurately weighed quantity of tolteridone tartarate and urea were mixed in a ratio 1:1, 1:2, 1:3 were taken in a china dish [14]. The ingredients were melted in a china dish and the contents of the china dish were allowed to cool on an ice bath. The

dispersion obtained was passed through the sieve and crushed in a mortar. The obtained solid dispersion was packed properly.

Preparation of solid dispersion by fusion method

Accurately weighed quantity of tolteridone tartarate and maltodextrin were mixed in a ratio 1:1,1:2,1:3 and were taken in a china dish. The ingredients were melted in a china dish and the contents of the china dish were allowed to cool on a ice bath. The dispersion obtained was passed through the sieve and crushed in a mortar. The obtained solid dispersion was packed properly.[13]

Pre -formulation studies:-

1. **Melting point determination:-**The melting point of the sample was determined by the capillary tube method.
2. **Ft-ir study:-** Infra red studies was carried out to rule out the interaction between drug and carrier used in formulation of solid dispersion by potassium bromide disc method using Infra red spectrophotometer. [15]

Evaluation of Solid Dispersion:-

1. **Thermal studies:-**It was carried out to ascertain the effect of heating on stability of the drug. It is based on thaw point melt method by heating drug in capillary melting point tube and allowing it to solidify. The melting point of rapidly solidifying mass was noted.
2. **Aqueous solubility studies:-** It was carried out to determine solubility of tolteridone tartarate alone in aqueous medium and also in presence of carriers like polyethylene glycol 6000 and polyvinyl pyrrolidone, urea, maltodextrin. This was done by dissolving excess drug in different flasks in different carriers.[14]
3. **Drug content :-**An amount equivalent to 2.0 mg of (TOL) of finely ground tablets was accurately weighed and transferred into 100 ml volumetric flask, the mixture was stirred for 30 minutes, then it was kept aside for five minutes and filtered using 0.5 µm filter paper, finally a certain portion of the filtrate was taken and then transferred into a series of 10 ml volumetric flasks. 1.0 ml of KMnO₄, and 2 ml Sulfuric acid solutions were pipetted, out then different volumes of (TOL) standard solution was added, the mixture was allowed to stand for 20 minutes then 2 ml of Methylene blue dye was added and finally water was added to make up the volume to 10.0 ml, then the absorbance of the solution was measured at 600 nm.[17]
4. **Percentage yield:** -Thoroughly dried solid dispersions were collected and weighed accurately. The percentage yield was then calculated using formulae given below
5. **Dissolution Studies:** The *invitro* dissolution studies were done to compare the rate of

dissolution of solid dispersions with that of pure drug Tolteridone tartarate and physical mixtures. The test was performed in USP paddle apparatus using 900ml acetate buffer solution at pH 4.0 and temperature 37± 10C at a stirrer depth of 50 rpm and the 5ml of the sample was withdrawn from the dissolution flask for a period of series of time intervals 5,10,15,30,45,60 mins respectively in order to maintain the sink condition. The withdrawn samples were estimated in uv-visible spectrophotometer at 600nm.

RESULTS AND DISCUSSION:

1. **Ft-ir study:-** Infra red spectral analysis showed that there was no interaction between pure drug and solid dispersion.
2. **Thermal study:-**Thermal study was carried out to ascertain the decomposition of drug. This indicated that there was no significant change in the melting point of tolteridone tartarate after thermal studies. The results are tabulated in table no: 3.
3. **Percentage yield:-**Percentage yield of different formulation was determined by weighing the solid dispersion after drying. The percentage yield of different formulation was in range of 43.5 - 82.2%
4. **Drug content analysis:-**Drug content of the solid dispersions was found to be in the range of 92 % and 98%. All the physical mixtures and solid dispersions showed the presence of high drug content, it indicates that the drug is uniformly dispersed in the powder formulation. Therefore, the method used in this study appears to be reproducible for preparation of solid dispersion.
5. **Solubility studies:-**Aqueous solubility studies indicated that solubility of tolteridone tartarate increased in presence of carriers when compared to solubility of drug in distilled water. The fast and rapid dissolution of drug observed in solid dispersions due to the presence of drug in amorphous form. The amorphous form has the highest energy compared to pure compound and produces faster dissolution. The other factors like absence of aggregation, good wettability and dispersability might have also contributed to the increase in dissolution rate. The results of aqueous solubility studies are given in table no:4
6. **Dissolution studies:-** In vitro dissolution studies indicated that as concentration of carrier increases, dissolution of drug improved. The formulation code F3 (Tolteridone tartarate : PEG 6000 = 1:3) showed 97 % release in 120 minutes than other PEG solid dispersions whereas the physical mixtures of same

formulation released 95.54% in 120 minutes, pure drug released only 28% in 120 minutes. Compared with the pure drug and physical mixture, the dissolution was found to increase in the following order.

Pure drug < Physical mixture < solid dispersion

This may be due to the presence of polymer, which increases wetting, and dissolution of the

drug. Even though the polymer is present in the physical mixture the dissolution rate was lesser than solid dispersion. This increase in dissolution rate of solid dispersion was attributed to molecular/ colloidal dispersion of drug in mixture. Higher the proportion of carrier there was a steep increase in dissolution rate of drug.

Table 1: Composition of tolteridone tartarate solid dispersions.

Formulation Code	Ingredients	Ratio of Solid Dispersion	Type of Dispersion
F1	Urea +Drug	1:1 1:2 1:3	solid dispersion
F2	Polyethylene glycol6000+Drug	1:1 1:2 1:3	solid dispersion
F3	Maltodextrin+Drug	1:1 1:2 1:3	solid dispersion
F4	Urea	1:1 1:2 1:3	physical mixture
F5	Polyethylene glycol6000	1:1 1:2 1:3	physical mixture
F6	Maltodextrin	1:1 1:2 1:3	physical mixture

Table 2: Thermal study of tolteridone tartarate solid dispersion.

S.NO	Melting point before thermal study	Melting point after thermal study
1	210	205
2	205	200
3	210	197

Table 3: Solubility studies of tolteridone tartarate solid dispersion.

Name of the carrier	Solubility of tolteridone in different polymers			
	0.25%	0.75%	1%	2%
PEG6000	10mg/ml	10mg/ml	10mg/ml	18mg/ml
Maltodextrin	8mg/ml	8mg/ml	7mg/ml	4mg/ml
urea	11mg/ml	12mg/ml	9mg/ml	7mg/ml

Table 4:- Percentage yield of tolteridone tartarate solid dispersion.

S.NO.	Formulation No.	% yield
1	F1	52.1
2	F2	60.9
3	F3	67.6
4	F4	56.0
5	F5	62.9
6	F6	61.6

Table 5:- %Drug content of tolteridone tartarate solid dispersion.

Formulation Batch	Drug Content
F ₁	95.87%
F ₂	92.23%
F ₃	98.33%
F ₄	96.73%
F ₅	98.67%
F ₆	91.12%

Table 6:-Dissolution profile of tolteridone tartarate solid dispersion.

S. No.	Batches	Cumulative % Release at Different Time Intervals in min							
		5	10	15	30	45	60	90	120
1	Tolteridone tartarate	1.343	3.122	4.871	6.442	14.11	16.87	19.79	28.92
2	F ₁	17.45	22.83	36.51	42.76	55.56	69.92	74.77	89.61
3	F ₂	18.12	23.55	37.11	45.23	67.44	72.12	86.88	97.73
4	F ₃	18.23	24.21	39.10	47.98	50.55	63.64	70.11	87.16
5	F ₄	15.56	20.11	33.01	40.44	50.75	65.11	73.88	91.90
6	F ₅	15.66	28.93	33.67	56.44	60.51	75.64	89.49	95.54
7	F ₆	17.23	29.12	34.67	47.55	53.88	69.09	74.66	80.56

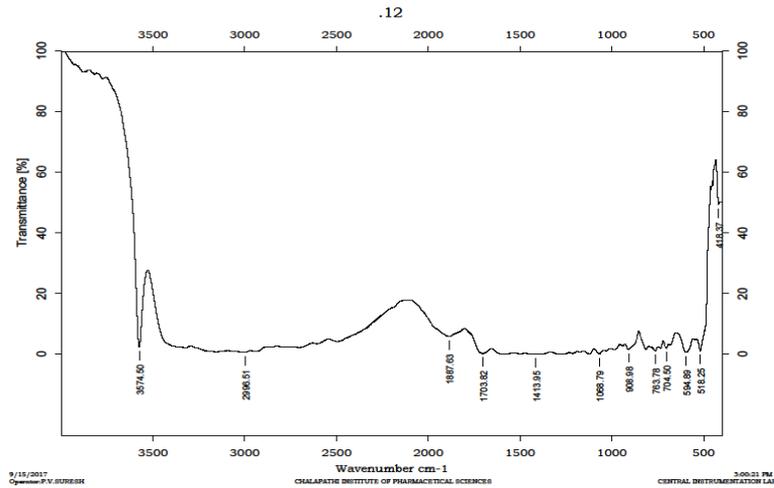


Fig 1:- Infrared spectrum of pure drug

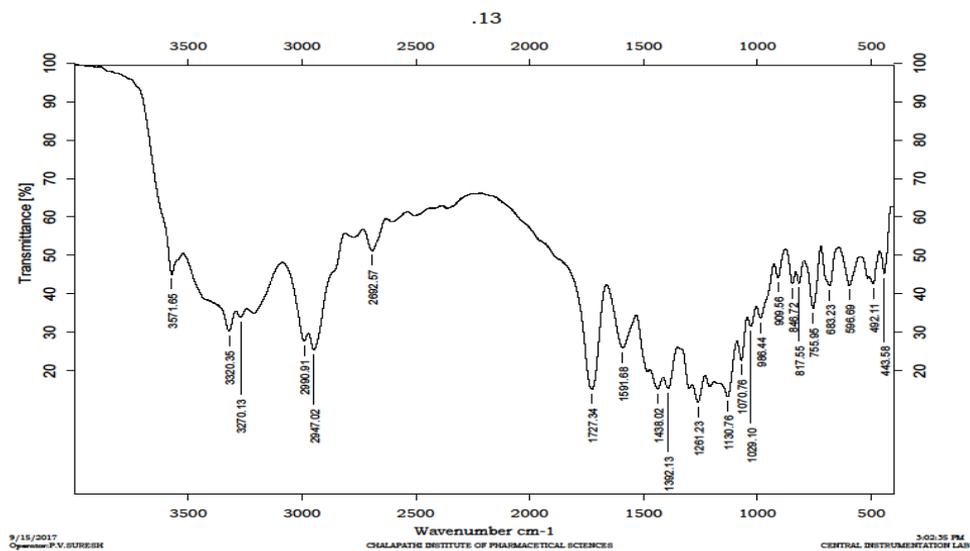


Fig 2: Infrared spectrum of drug and polymers

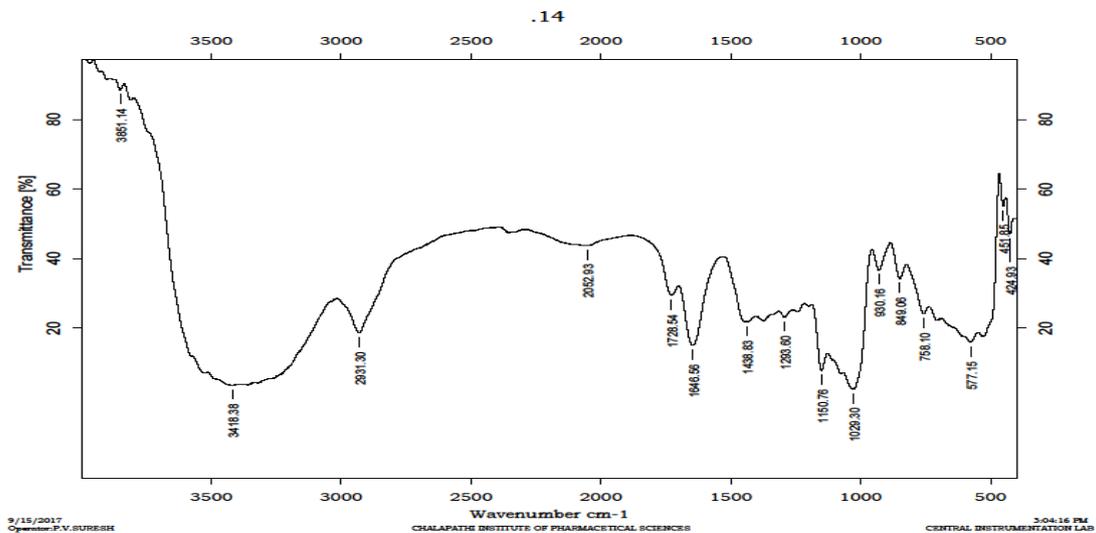


Fig 3: Infrared spectrum of all the polymers

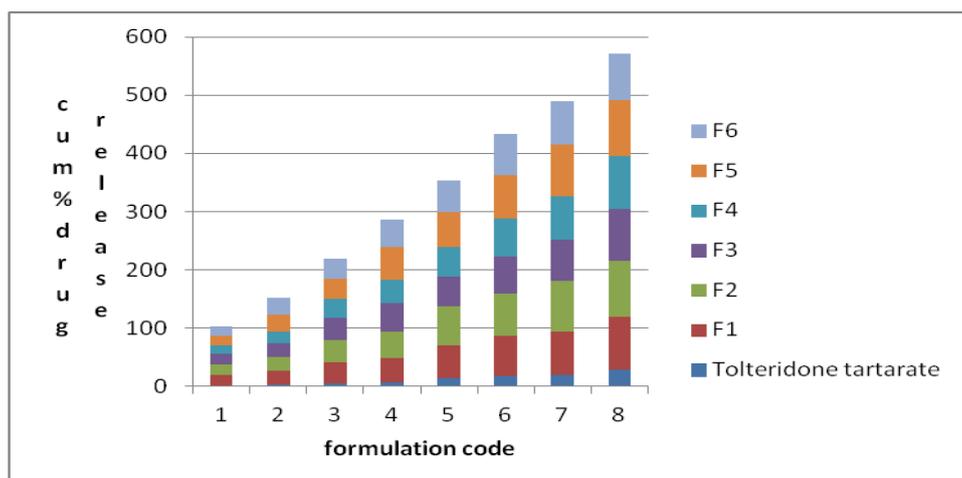


Fig 4:-dissolution profile of solid dispersions.



Fig 5: Solid dispersion of tolteridone tartarate using different polymers.

CONCLUSION:

Concept of solid dispersion is very easy approach for solubility enhancement when compared with other approaches. So we conclude that solubility of poorly water soluble drugs, stability of unstable drugs and thereby bioavailability can be successfully enhanced by solid dispersion technique based on reported literature. The increase in bioavailability of drug is because of higher solubility enhancement. The higher solubility of solid dispersions is because of conversion of crystalline drug to amorphous form. Among all the solid dispersions prepared the dispersion with PEG6000 was found to be the best formulation and it was found to be the best carrier for the preparation of solid dispersion.

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