Research Article

Formulation and Evaluation of Solid Dispersion of Melitracen

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ABSTRACT

Melitracen is an antidepressant drug is widely used for depression. One of the major problems with this drug is its very low solubility in biological fluids, which results into poor bioavailability after oral administration. In the present study, an attempt has been made to increase solubility of Melitracen by solid dispersion technique. The solid dispersions were evaluated percentage yield, phase solubility study, drug content and *in vitro* dissolution studies. The best formulation of solid dispersion was compressed into fast dissolving tablets using crosspovidone by direct compression technique. The prepared tablets were evaluated for precompression and post compression parameters. The prepared tablet formulation (ST) showed complete release of drug in 30 min. Accelerated stability study was conducted for the formulations ST which showed no significant difference in the drug content, disintegration time, hardness friability and *in vitro* dissolution profiles. These results revealed that fast dissolving tablets of poorly soluble drug Melitracen, showing enhanced solubility and dissolution rate and hence better patient compliance

Keywords: Melitracen, polyethylene glycol 6000, polyethylene glycol 4000, β-cyclodextrin.

INTRODUCTION

Oral drug delivery is one of the simple and easy modes of drug administration. Because of the better stability, smaller bulk, accurate dosage and easy production, solid oral dosages forms offer many advantages over other types of oral dosage forms. Hence, most of the new chemical entities (NCEs) that are developed these days are intended to be used as a solid dosage form that can produce an effective and reproducible in vivo plasma concentration after oral administration. However, many of the NCEs developed for oral administration are poorly water soluble and less-absorbed, which can affect the drug's inherent efficacy. Moreover, most promising NCEs, despite their high permeability, are generally absorbed in the upper small intestine only, absorption being reduced significantly after the ileum, showing, therefore, that there is a small absorption window. Consequently, if these drugs are not completely released in this region of the gastrointestinal tract (GIT), they will have a low bioavailability. Therefore, one of the major concentration and challenges for pharmaceutical industry in formulating an oral solid dosage form is to improve the solubility of drugs and the necessity for suitable approaches and strategies[1].

The enhancement of oral bioavailability of poorly soluble drugs remains one of the most challenging aspects of drug development. The rate and extent of dissolution of the active ingredient from any solid dosage form determines rate and extent of absorption of the drug. In the case of poorly soluble drugs dissolution is the rate limiting step in the process of drug absorption. Potential bioavailability problems are arising with extremely hydrophobic drugs due to incomplete absorption from the GIT. The concept of solid dispersion has been widely and successfully applied to improve the solubility, dissolution rate and consequently the bioavailability of poorly soluble drugs. In solid dispersion method drug is dispersed in inert water soluble carrier at solid state. Solid dispersion is a process in which one or more active ingredients are dispersed in an inert carrier or matrix of solid state prepared by melting (fusion), melting solvent method.

With recent advances in molecular screening methods for identifying potential drug candidates, an increasing number of poorly

water-soluble drugs are being identified as potential therapeutic agents. In fact, it has been estimated that

40% of new chemical entities currently being discovered are poorly water-soluble. Unfortunately, many of these potential drugs are abandoned in the early stages of development due to solubility concerns. It is therefore becoming increasingly more important that methods for overcoming solubility limitations be identified and applied commercially such that the potential therapeutic benefits of these active molecules can be realized[2]. Melitracen is an antidepressant drug is widely used for depression. One of the major problems with this drug is its very low solubility in biological fluids, which results into poor bioavailability after oral administration. In the present study, an attempt has been made to increase solubility of Melitracen using solid dispersion technique using polyethylene glycol 6000 (PEG 6000), polyethylene glycol 4000 (PEG 4000), mannitol and β-cyclodextrin by solvent evaporation and kneading method.

MATERIALS AND METHODS

MATERIALS

Melitracen was obtained as gift sample from Microlabs Pvt Ltd Bangalore, India. β cyclodextrin, PEG 4000, PEG 6000, Mannitol from Loba Chemicals Pvt. Ltd., Mumbai, India.

METHODS

Solvent evaporation and Kneading method

For solvent evaporation, drug and carriers (PEG 4000, PEG 6000, mannitol) were weighed in the ratio of 1:1, 1:2 and 1:3. The physical mixture was prepared by mixing drug and carrier in a mortar. Solid mass was pulverized and passed through sieve no.80 to get uniform sized particles. Physical mixture of Melitracen and carriers (PEG 4000, PEG 6000 and mannitol) in ratios 1:1, 1:2 and 1:3 were dissolved in sufficient amount of methanol. Then the solvent was evaporated using solvent evaporation method on water bath. Lastly the dried mass obtained was pulverized and sieved through sieve no 60 and the fraction was collected.

For kneading method, drug and carrier β-Cyclodextrin were weighed in the ratio of 1:1, 1:2 and 1:3. The physical mixture was prepared by mixing drug and carrier in a mortar.Solid mass was pulverized and passed through sieve no.80 to get uniform sized particles.The physical mixture of Melitracen and β-Cyclodextrin in different ratio (1:1, 1:2, 1:3) were triturated using small quantity of methanol and water mixture (1:1w/w) separately.The slurry was kneaded for 45 minutes and dried at 45 ^{o}C.The dried mass was pulverized and sieved through sieve no 60 and the fraction was collected[3,4]. The compositions of different solid dispersions of Melitracen are show in **Table 1.**

Table 1: Composition of solid dispersions of Melitracen

Solid dispersion composition	Method	Drug-Polymer ratio	Formulation Code
Melitracen: Polyethylene glycol 4000	Physical mixture	1:1	PM1*
		1:2	PM2*
		1:3	PM3*
	Solvent evaporation method	1:1	SD1**
		1:2	SD2**
		1:3	SD3**
Melitracen: Polyethylene glycol 6000	Physical mixture	1:1	PM4*
		1:2	PM5*
		1:3	PM6*
	Solvent evaporation method	1:1	SD4**
		1:2	SD5**
		1:3	SD6**
Melitracen: Mannitol	Physical mixture	1:1	PM7*
		1:2	PM8*
		1:3	PM9*
	Solvent evaporation method	1:1	SD7**
		1:2	SD8**
		1:3	SD9**
Melitracen: β-Cyclodextrin	Physical mixture	1:1	PM10*
		1:2	PM11*
		1:3	PM12*
	Kneading method	1:1	SD10**
		1:2	SD11**
		1:3	SD12**

***PM, physical mixture; **SD; solid dispersion**

Preparation of fast dissolving tablets of Melitracen solid dispersion by direct compression method

Solid dispersion of Melitracen with βcyclodextrin(1:3 ratio) equivalent to 20mg of drug prepared by kneading method were taken and mixed with directly compressible diluent, superdisintegrants and other excipients in a plastic container. Table 2 gives compositions of the tablet formulations. Powder blend were directly compressed using 10.05 mm, round-shaped flat punch in a single station tablet compression machine[5].

Table 2: Composition of fast dissolving tablets of Melitracen solid dispersion

Ingredients (mg/tablet)	Solid dispersion tablet (ST)
Solid dispersion	120
Crospovidone	15
Microcrystalline cellulose	59
Magnesium stearate	2
Talc	4
Total	200

Evaluation of Melitracen solid dispersion systems

Percent Practical Yield (PY)

Percentage practical yield were calculated to know about percent yield or efficiency of any method, thus its help in selection of appropriate method of production.Solid dispersions were collected and weighed to determine practical yield (PY) from the following equation[6].

PY (%) = Practical Mass (SD) / Theoretical Mass (Drug + Carrier) × 100

Phase solubility study

Solubility studies were performed according to the method described by Higuchi and Connors.An excess amount of Melitracen in distilled water and Melitracen containing different concentration of carrier in 20 ml of 0.1NHCl was placed in conical flask.All flasks were closed with stopper and covered with cellophane membrane to avoid solvent loss. The content of the suspension was equilibrated by shaking for 72 hrs in a mechanical shaker at room temperature.After attainment of equilibrium, the content of that flask was then filtered through 0.45mm filter. The filtrate was diluted and assayed spectrophotometrically (Shimadzu 1700 UV-Visible spectrophotometer) at 286 nm. All solubility measurement was performed triplicate[7].

Drug content

In each case PMs and solid dispersion system, sample equivalent to 50 mg of Melitracen was accurately weighed and transferred to 50 ml volumetric flask and extracted in 0.1N HCl. The volume was made up to 50 ml with 0.1N HCl.From this 1ml is subsequently diluted to 100 ml with 0.1N HCl and assayed for Melitracen content by measuring at 286 nm using 0.1N HCl as blank.The Melitracen content was calculated from the calibration curve.The experiments were conducted in triplicate[5].

***In vitro* drug release studies**

The quantity of solid dispersion equivalent to 20mg of Melitracen was filled in colourless hard gelatin capsule by hand filling method.The dissolution study of capsules was conducted using dissolution testing USP apparatus 1 (basket method) in 900 ml of HCl acid buffer of pH 1.2 at 37 ± 0.5ºC and at a speed of 50 rpm.Aliquot of 5ml was withdrawn at predetermined time interval and equivalent amount of fresh medium was replaced to maintain a constant volume after each sampling and analyzed spectrophotometrically at 286nm using UV Visible spectrophotometer[5].

Evaluation parameters for fast dissolving tablets of solid dispersion of melitracen

Precompression Parameters

The flow properties of granules (before compression) were characterized in terms of angle of repose, compressibility index and Hausner ratio. Angle of repose was performed using funnel method by keeping a funnel vertically in a stand at a specified height above a paper placed on a horizontal surface. The funnel bottom was closed and 10 gm of powder was filled in the funnel. Then the funnel was opened to releases the powder on the paper to form a smooth conical heap. The radius of the heap (r) and the height of the heap (h) were measured[8]. The $\tan^{-1}$ of the height of the pile / radius of its base gave the angle of repose. Bulk density (ρb) and tapped densities (ρt) were determined and thereby Hausner ratio (H_R) and compressibility index were calculated according to the following equations[9].

Compressibility index = 100 (ρ tapped – ρ bulk) / ρ tapped

Hausner ratio = ρ tapped / ρ bulk

Hardness

Hardness (diametric crushing strength) is a force required to break a tablet cross the

diameter.The hardness of a tablet is an indication of its strength.The tablet should be stable to mechanical stress during handling and transportation.The degree of hardness varies with the different manufactures and with the different types of tablets.The hardness was tested by using Monsanto hardness tester.The averages of five determinations were taken[10].

Weight variation

Weight variations were tested in 10 different randomly selected individual tablets from each batch.Weight variations were measured by digital electronic balance (Citizen D 1262, India).The averages of ten determinations were taken; weight variation can be calculated by[10],

$$PD = \frac{W(avg) - W(initial)}{W(avg)} \times 100$$

Where PD= Percentage deviation

$W_{(avg)}$ = Average weight of table

$W_{(initial)}$ = Individual weight of tablet

Friability

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface.This in process quality control test is performed to ensure the ability of tablets to withstand the shocks during processing, handling, transportation, and shipment.Permitted friability limit is 1.0 %.Roche friabilator (Ketan, Mumbai) was used to measure the friability of the tablets.Ten tablets were weighed collectively and placed in the chamber of the friabilator.In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator.It was rotated at a rate of 25 rpm.After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively[10].

$$F = \frac{W(initial) - W(final)}{W(initial)} \times 100$$

Drug content

Ten tablets were crushed and powdered.Weighed accurately the quantity equivalent to 25 mg of drug and taken in 25 ml volumetric flask and dissolved with small quantity of 0.1N HCl (pH 1.2) and volume made up to the mark with same medium and stirred for 12 hrs.After stirring, 1 ml solution was withdrawn and filtered through 0.45µm Whatman filter paper and volume made up to 100 ml of water.The absorbance was measured and at 286 nm using UV Spectrophotometer[11].

$$\text{Drug content} = \text{Concentration} \times \text{Dilution Factor}$$

$$\%\text{Drug content} = \frac{\text{Drug content (mg)}}{\text{Label Claim(mg)}} \times 100$$

Wetting time

A piece of tissue paper folded twice was placed in a small petridish (I.D = 6.5 cm) containing 10 ml of water, a tablet was put on the paper, and the time for complete wetting was measured.Three trials from each batch were performed and standard deviation was also determined[12].

***In vitro* disintegration time**

In vitro disintegration time was determined using disintegration test apparatus.A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube.The water was maintained at a temperature of 37 ± 0.5 ºC and time taken for complete disintegration of the tablet with no palpable mass remaining i the apparatus was measured in seconds[13].

***In vitro* dissolution studies**

In-vitro dissolution study was performed by using USP dissolution testing appartus 2 (Paddle method).Weighed tablets were kept in a flask of the dissolution apparatus containing 900 ml of 1.2 pH HCl acid buffer dissolution medium maintained at 37 ± 0.5ºC and at a speed of 50 rpm.Aliquot of dissolution medium (5 ml) was withdrawn at specific time intervals and the samples were replaced with fresh dissolution medium.Aliquot were analyzed spectrophotometrically at 286 nm against suitable blank using UV-visible spectrophotometer[14].

Stability studies

Stability studies were carried out according to ICH guidelines for the best formulations SD12 by exposing the formulation in their final packing mode to the temperature 40 ± 2°C and relative humidity 75±5 % in programmable environmental test chamber Aliquot were withdrawn at 30, 60 and 90 days and analyzed for change in drug content, hardness, friability, disintegration time and *in-vitro* dissolution profile[15].

RESULTS AND DISCUSSION

Evaluation of Melitracen solid dispersions

Saturation Solubility Study

The solubility studies of Melitracen and solid dispersion systems are studied in distilled water. The results were shown in Table 3. The solubility of Melitracen from solid dispersions

prepared by all methods shows solubility in order, β-Cyclodextrin > PEG 6000 > PEG 4000 > mannitol > pure drug in all ratios. Future solid dispersions showed better solubility than physical mixtures corresponding to the carriers in above order. The solubility of Melitracen in distilled water is about 0.224±0.13 µg/ml. The minimum solubility (1.143±0.21) of Melitracen was found in the physical mixture with mannitol in 1:1 ratio and the maximum solubility (3.004±0.29 µg/ml) was found in solid dispersion with β-Cyclodextrin in 1:3 ratio.

Table 3: Solubility of Melitracen from physical mixtures and its solid dispersion systems prepared with PEG 4000, PEG 6000, mannitol and β-Cyclodextrin

Carrier	Code	Drug/Carrier Ratio	Method	Melitracen concentration (µg/ml) ±SD
Melitracen	-	-	-	0.224±0.13
PEG 4000	PM1	1:1	Physical mixture	1.380±0.15
	PM2	1:2	Physical mixture	1.487±0.32
	PM3	1:3	Physical mixture	1.643±0.25
PEG 6000	PM4	1:1	Physical mixture	1.754±0.57
	PM5	1:2	Physical mixture	1.897±0.23
	PM6	1:3	Physical mixture	1.976±0.19
Mannitol	PM7	1:1	Physical mixture	1.115±0.19
	PM8	1:2	Physical mixture	1.143±0.21
	PM9	1:3	Physical mixture	1.276±0.15
β-Cyclodextrin	PM10	1:1	Physical mixture	2.157±0.06
	PM11	1:2	Physical mixture	2.276±0.16
	PM12	1:3	Physical mixture	2.476±0.47
PEG 4000	SD1	1:1	Solvent evaporation	1.795±0.63
	SD2	1:2	Solvent evaporation	1.896±0.54
	SD3	1:3	Solvent evaporation	1.996±0.91
PEG 6000	SD4	1:1	Solvent evaporation	2.132±0.32
	SD5	1:2	Solvent evaporation	2.542±0.71
	SD6	1:3	Solvent evaporation	2.846±0.49
Mannitol	SD7	1:1	Solvent evaporation	1.379±0.41
	SD8	1:2	Solvent evaporation	1.411±0.57
	SD9	1:3	Solvent evaporation	1.699±0.49
β-Cyclodextrin	SD10	1:1	Kneading	2.654±0.51
	SD11	1:2	Kneading	2.982±0.31
	SD12	1:3	Kneading	3.004±0.29

Percent Practical yield and Drug content

Solid dispersions of Melitracen were prepared by different method using carriers like PEG-4000, PEG-6000, mannitol and β-Cyclodextrin. In the present work, total 24 formulations were prepared in which 12 formulations were physical mixtures of drug and carriers (PM1-PM12) and others 12 formulations were the solid dispersions (SD1-SD12). Solid dispersion prepared by two technique i.e., solvent evaporation method and kneading method. The results of percent practical yield and drug content studies are shown in **Table 4**. The % Practical yield of the prepared solid dispersions was found to be in the range of 84.95– 98.95. The maximum yield was found to be 98.95% in SD12. The drug content of the prepared formulations was found to be in the range of 93.21-99.57 % indicating the application of the present methods for the preparation of Solid dispersions with high content uniformity. The maximum % drug content was found to be 99.57 % in SD12.

Table 4: Percentage practical yield, drug content uniformity of Physical Mixture and Solid Dispersion of Melitracen with by PEG 4000, PEG 6000 and mannitol

Carrier	Code	Drug/Carrier Ratio	% Practical Yield	Drug Content * (%)
Melitracen	-	-	-	-
PEG 4000	PM1	1:1	86.23	93.87
	PM2	1:2	88.21	94.65
	PM3	1:3	89.35	96.56
PEG 6000	PM4	1:1	92.11	95.87
	PM5	1:2	92.54	96.65

	PM6	1:3	93.65	97.24
Mannitol	PM7	1:1	84.95	93.21
	PM8	1:2	85.84	94.76
	PM9	1:3	86.22	96.65
PEG 4000	SD1	1:1	89.32	96.87
	SD2	1:2	90.83	96.95
	SD3	1:3	91.97	98.36
PEG 6000	SD4	1:1	93.12	97.64
	SD5	1:2	93.75	98.25
	SD6	1:3	95.24	99.11
Mannitol	SD7	1:1	85.87	96.18
	SD8	1:2	86.96	96.45
	SD9	1:3	88.87	97.85
β-Cyclodextrin	PM10	1:1	93.95	97.12
	PM11	1:2	94.78	97.45
	PM12	1:3	95.18	98.74
β-Cyclodextrin	SD10	1:1	97.11	99.11
	SD11	1:2	97.28	99.24
	SD12	1:3	98.95	99.57

***In vitro* drug release study**

The in vitro dissolution study of different formulation is shown in Figure 1 and 2. It was found that the *in vitro* drug release of physical mixtures and solid dispersions from all the formulation was more than 29.80 ± 1.8% and 56.20±2.6% respectively within 120 minutes as compared to pure Melitracen which shows only 22.19 ± 0.02 % of drug release. The highest *in vitro* drug release was observed with β-Cyclodextrin solid dispersion in ratio 1:3 (SD12) 94.24 ± 2.3 % hence selected as best formulation. The *in vitro* drug release was increased in the manner of pure drug < mannitol <PEG-4000< PEG-6000< β-Cyclodextrin. Fom the results of *in vitro* drug release, the formulation SD12 was selected as the best formulation and compressed into fast dissolving tablets of Melitracen (ST) for further studies.

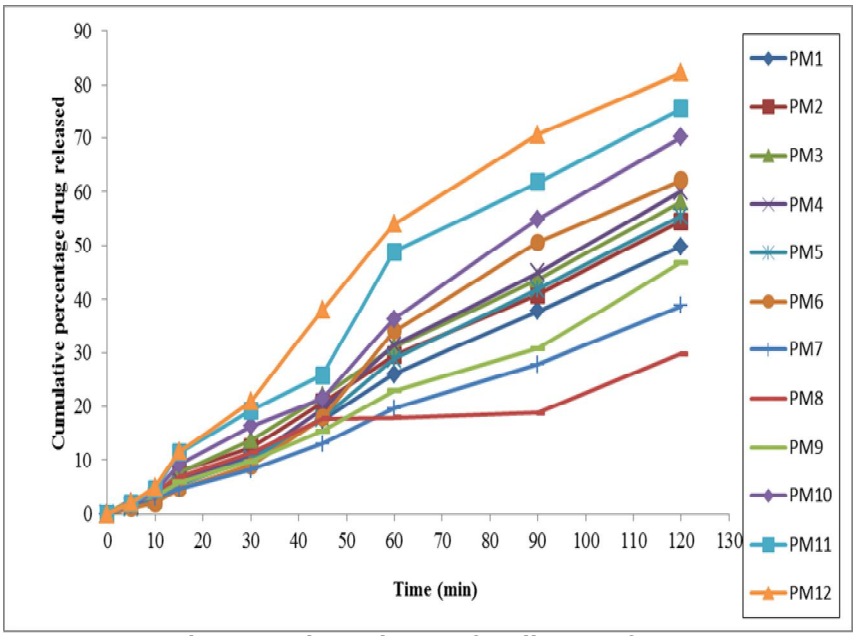

Fig. 1: *In vitro* release of Melitracen from different formulations PM1-PM12

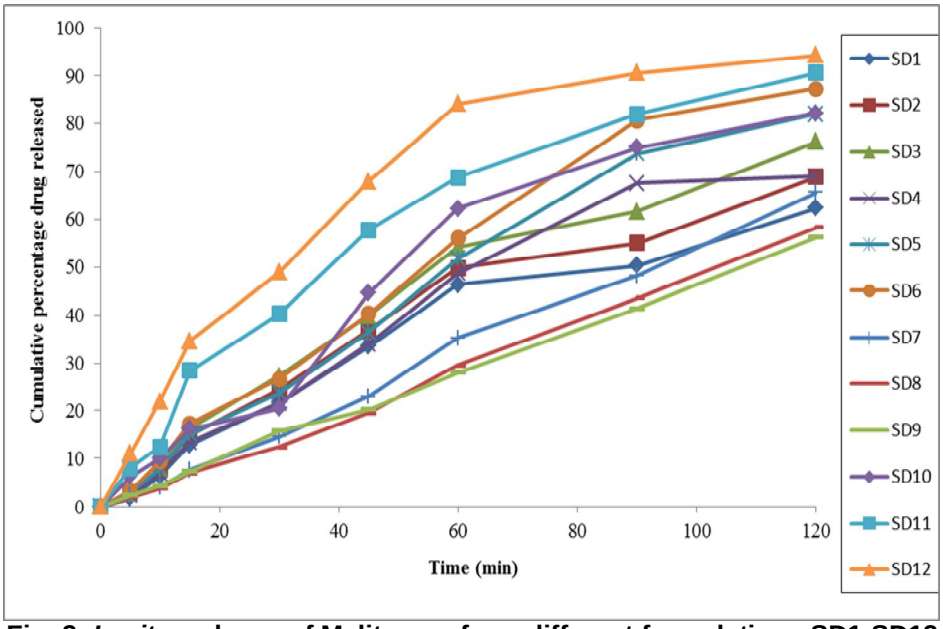

Fig. 2: *In vitro* release of Melitracen from different formulations SD1-SD12

Evaluation parameters for fast dissolving tablets of Melitracen: β Cyclodextrin solid dispersion (ST)

Pre-compression evaluations

Bulk density, Tapped density, Carr's index and Angle of repose

Pre-compression parameters play an important role in improving the flow properties of pharmaceuticals especially in tablet formulation. These include bulk density, tapped density, Carr's index, Hausner ratio and Angle of repose. Before formulation of fast dissolving tablets, the drug and ingredients were evaluated for all the above said parameters and it was found that all the observations were within the prescribed limits of IP. Precompression parameters of formulation ST are shown in **Table 5**. The bulk density and Tapped density of the formulation was found as 0.73±0.006g/ml and 0.82±0.024g/ml respectively. Carr's index value for the formulation was 3.38±0.24 and angle of repose has been used as indirect method of quantifying power flow ability, and had a value of 28.65±1.02 for the formulation. All the formulations were fallen in good flow character based on angle of repose, compressibility index and Hausner ratio reports.

Table 5: Precompression Parameters of fast dissolving tablets of Melitracen solid dispersion

Formulation code	Bulk density (g/ml)	Tapped density (g/ml)	Angle of repose°	Carr's index (%)
ST	0.76	0.79	29.82	3.79
	0.73	0.83	28.86	2.83
ST1	0.71	0.85	27.98	3.53
Mean±SD*	0.73±0.006	0.82±0.024	28.65±1.02	3.38±0.24

*Values are mean ± SD, n=3

Post-compression evaluations

Weight variation, hardness, friability, drug content, and Disintegration time

Post-compression parameters of Melitracen solid dispersion tablet (ST) are showed in Table 6. Weight variation and friability of tablets had a value 199.35±1.12 mg and 0.40±0.009 respectively. The hardness values of tablets were found as 3.18±0.12 Kg/cm^2 respectively. Drug content for the tablet was found as 98.97±0135%. Further Disintegration time value for the tablets came as 37.87±1.32 respectively.

Table 6: Post compression Parameters for fast dissolving tablets (ST) of Melitracen solid dispersion

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Weight variation (mg)	Drug content (%)	Disintegration time (sec)
ST	3.20	0.42	199.46	98.86	36.99
	3.53	0.48	198.24	99.09	37.43
	2.81	0.31	200.35	98.98	39.21
Mean±SD*	3.18±0.12	0.40±0.009	199.35±1.12	98.97±.0135	37.87±1.32

*Values are mean ± SD, n=3

***In vitro* drug release**

The cumulative drug release of the formulation ST (**Figure 3**) was carried out by the procedure mentioned earlier. The tablets were carried out for the release studies for 30 min. The % cumulative drug release obtained for the formulation (ST) was 99.50±0.28% at the end of 30 min.

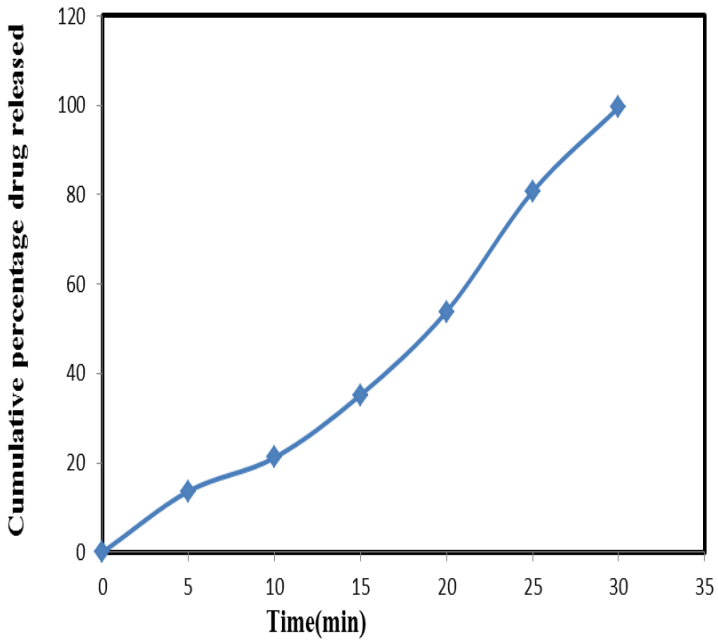

Fig. 3: *In vitro* dissolution profile fast dissolving tablets (ST) of Melitracen solid dispersion

Accelerated stability studies

During and at the end of the accelerated stability study, the tested tablets showed non-significantly different drug content from that observed at the beginning of the study. They also showed satisfactory *in vitro* drug release values during and at the end of the accelerated study period. Accelerated stability of the formulation ST was carried at 40 ± 2°C / 75 ± 5% R.H for a period of 3 months and the samples were tested for drug content and *in vitro* drug release for every month and results were shown in Table 7.

Table 7: Accelerated stability study of formulation ST

Time	Drug content* (%)	*In Vitro* drug release at 30 min
I st month	98.87±.0135	99.50±0.28
II nd Month	98.66±0.671	99.94±0.52
III rd Month	98.32±0.121	99.72±0.26

*Values are mean±SD, n=3.

CONCLUSIONS

From the above studies it is concluded that the solid dispersion technique may be useful to improve solubility, dissolution rate and subsequently bioavailability of poorly soluble drug. The concept of formulating fast dissolving tablets of Melitracen solid dispersion using superdisintegrant offers a suitable and practical approach in serving desired objectives of faster disintegration and dissolution characteristics. The *in vitro* studies showed that this is a potential drug delivery for Melitracen with a considerably good release profile and future studies are warranted to confirm these results *in vivo*.

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