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NOVEL APPLICATION OF MIXED HYDROTROPIC SOLUBILIZATION TECHNIQUE IN THE FORMULATION AND EVALUATION OF SOLID DISPERSION OF FLUPIRTINE MALEATE

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ABSTRACT

Flupirtine is an amino pyridine derivative that functions as a centrally acting non-opioid, non-steroidal analgesic. It is a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties. Its muscle relaxant properties make it popular for back pain and other orthopedics uses. In the present investigation, recently developed mixed hydrotropic solid dispersion technology precludes the use of organic solvent and also decreases the individual concentration of hydrotropic agents, simultaneously decreasing their toxic potential. Mixed-hydrotropic solubilisation technique is the experience to increase the solubility of poorly water soluble drugs in the aqueous solution containing blends of hydrotropic agents, which may give synergistic enhancement effect on solubility of poorly water-soluble drugs and to reduce concentrations of each individual hydrotropic agent to minimize their toxic effects due to high concentration of hydrotropic agents. The Flupirtine loaded solid dispersion was prepared by a solvent evaporation technique using sodium benzoate and a niacinamide hydrotropic mixture. The prepared solid dispersions were valuated regarding their solubility, mean particle size, in-vitro drug release. The prepared solid dispersions were found very stable (chemically). The superior dissolution rate due to its reduced particle size may have contributed to the increased oral bioavailability. This study demonstrated that mixed-solvency may be an alternative approach for poorly soluble drugs to improve their solubility and oral bioavailability.

Keywords: Flupirtine, Solid dispersion, Mixed-hydrotropic solubilisation, Solvent evaporation technique, Sodium benzoate, Niacinamide

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INTRODUCTION

Poor aqueous solubility as well high intra- and inter subject inconsistency are considered to be main barricades for poor oral bioavailability. A number of formulation approaches, such as solid dispersions, salt formation, micronization, cyclodextrin complexation, micellar solutions, nanoparticulates to improve the oral absorption of drugs[1, 2]. Hydrotropy is one of the recognized techniques available to enhance the aqueous solubility of a drug. It has a well-known impending of improving the solubilities and dissolution profiles of hydrophobic drugs[3, 4]. It is an another approach for the delivery of drugs, which is attached with drugs having a low water solubility and poor oral bioavailability[5].Hydrotropy is a molecular occurrence, where by adding a second solute (hydrotrope) helps to increase the aqueous solubility of poorly soluble solutes. Simply the existence of a large quantity of one solute enhances the solubility of another solute [6, 7]. Hydrotropes have an amphiphilic molecular structure, which contains

both hydrophilic and a hydrophobic portions. The competence of hydrotropic solubilization depends on the balance between the hydrophobic and hydrophilic fractions[8, 9]. Different association patterns of hydrotrope assemblies and unique geometrical features distinguish them from other solubilizers[10]. Improvement in the aqueous solubility by a hydrotrope is based on the molecular self-association of the hydrotrope with solute molecules[11]. Solid dispersion technology is one of the methods of increasing the dissolution rate and therefore the rate of absorption or total bioavailability of poorly water-soluble drugs. The common methods of making solid dispersions are solvent evaporation, fusion, and fusion-solvent methods[12-14]. Flupirtine, ethyl-*N*-[2-amino-6-(4-fluoro-phenylmethyl-amino) pyridine-3-yl] carbamate, is a non-opioid analgesic without antipyretic or antiphlogistic properties. It acts centrally on γ-aminobutyric acid a receptors and the selective neuronal Kv7 potassium channel[15-17], thus offering a mechanism-based therapy for pain relief and normalization of muscle tension. In patients with acute and chronic pain, flupirtine is clinically as efficient as weak opioids and NSAIDs [18-21], and its well-known neuro protective properties make this drug a possible candidate for the treatment of Alzheimer's, Creutzfeldt–Jakob's and Parkinson's, disease and other neurodegenerative disorders [22-25].

The objective of the present study was to formulate and evaluate flupirtine containing solid dispersion. A sodium benzoate and niacinamide hydrotropic mixture was utilized.

MATERIALS AND METHODS

Materials:

Flupirtine Maleate was obtained as a gift sample from ZCL Chemical Limited Ankleshwar, India Sodium benzoate, sodium acetate; sodium citrate, urea and niacinamide were purchased from Sigma-Aldrich (Mumbai, India). All other chemicals and reagents used were of analytical grade. Double distilled water was prepared freshly and used whenever required.

Method:

Solubility study:

An excess quantity flupirtine of was added to screw capped 10.0 mL glass vials containing the different aqueous systems composed of distilled water and various hydrotropic solutions of different concentrations in water. The resultant mixture was shaken vigorously for10.0 min and stirred on a magnetic stirrer plate at room temperature for 12 h. After the 12 h period elapsed, samples were withdrawn and centrifuged at 10,000 RPM for 15.0 min. The supernatant of each batch was filtered through 0.45µm membrane filters. The filtrates were suitably diluted and analysed using a UV spectrophotometer (Systronics 2202 India) at 304 nm. The results of triplicate measurements and their means were reported.

Preparation of solid dispersions by a mixed solvency approach:

The solid dispersion of flupirtine was prepared with hydrotropic agent using a solvent evaporation technique. Concisely, different amounts of hydrotropic agents {sodium benzoate (5 gm) and niacinamide (5 gm.)} were suspended in 50 mL of aqueous flupirtine (2.5 g) solution. After the addition of hydrotropic agents, the resultant mixture was subjected to evaporation (wet). The wet product obtained from the evaporation step was dried in an oven set at 50 ± 2◦C to remove any remaining moisture. The resultant solid dispersions were passed through a #100 mesh. The prepared solid dispersions were stored in desiccators until their further evaluation. The physical mixtures were prepared in same the ratio triturating the drug and hydrotropic agent in a porcelain mortar. The physical mixtures were passed through a #100 mesh and stored in an air tight glass bottle until their further evaluation. The compositions of the solid dispersion and physical mixtures are given in Table 1 & 2.

Table 1: Composition of solid dispersions of flupirtine maleate

S. no.	Solid dispersion	Drug: solubilizers	Quantity taken (gm)				
			FM	SB	NM	SCI	ST
1	SDA	1:4	2.5	5	2.5	2.5	-
2	SDB	1:3.33	2.4	4.0	2.0	2.0	-
3	SDC	1:3	1.6	2.4	-	-	2.4
4	SDD	1:2	2.4	3.2	1.6	-	-
5	SDE	1:3	3.2	4.8	4.8	-	-
FM= Flupirtine maleate; SB= Sodium benzoate; NM= Niacinamide; SCI= Sodium citrate; ST= PEG 6000.							

Table 2: Composition of physical mixtures of flupirtine maleate

S. No.	Physical mixture	Drug: solubilizers	Quantity taken (gm)				
			FM	SB	NM	SCI	ST
1	PMA	1:4	2.5	5	2.5	2.5	-
2	PMB	1:3.33	2.4	4.0	2.0	2.0	-
3	PMC	1:3	1.6	2.4	-	-	2.4
4	PMD	1:2	2.4	3.2	1.6	-	-
5	PME	1:3	3.2	4.8	4.8	-	-
FM= Flupirtine maleate; SB= Sodium benzoate; NM= Niacinamide; SC= Sodium citrate; ST= PEG6000.							

Characterization of the Prepared Solid Dispersion:

Drug content and percentage yield:

The drug contents and percentage yields of the solid dispersion and physical mixtures were determined. The samples were dissolved in a suitable quantity of distilled water and the drug content was determined by a UV spectrophotometer (Systronics 2202 India) at 304 nm.

In-vitro dissolution study:

The in-vitro dissolution studies were performed to conclude the rates of dissolution of the drug alone, solid dispersion and physical mixtures. The dose equivalent to 100.0 mg was used for the dissolution study. The dissolution test was executed in an U.S.P. XXIV (type II) dissolution test apparatus (Model TDT6P, Electrolab Mumbai, India) with paddle to rotate at 50 r.p.m using 900.0 mL of demineralised water was taken as dissolution medium. The temperature of the medium was kept at 37 ± 0.5◦C throughout the experiment. A 10 mL aliquot was withdrawn at predetermined time intervals of 2, 5, 10, 15, 30, 45 and 60 min and filtered through 0.45 µm filters. Then, 10 mL of fresh dissolution medium was replaced to maintain the constant volume of dissolution medium. The filtrates were analysed using a UV spectrophotometer (Systronics 2202 India) at 304 nm. The results of triplicate measurements and their means were reported.

Micromeritic Properties of Solid Dispersions:

Bulk density:

It is defined as the mass of many particles of the material divided by the total volume they occupy. The total volume includes particle volume, inter-particle void volume, and internal pore volume. The bulk density of the formulated granules was evaluated using bulk density apparatus. It is expressed in gm/ml and is given by

$$\text{Bulk density} = \frac{\text{Mass of powder (M)}}{\text{Volume of the bulk powder (Vb)}}$$

Tapped density:

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gm/ml and is given by:

$$\text{Tapped density} = \frac{\text{Mass of powder (M)}}{\text{Tapped volume of powder (Vt)}}$$

Compressibility index and hausner ratio:

The compressibility index and hausner's ratio are measures of the propensity of a powder to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula:

$$\text{Carr's index (I)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}}$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Angle of repose:

Angle of repose was determined by Neumann's method and calculated using the formula, for un lubricated as well as lubricated granules.

$$\text{Tan}\theta = h/r$$

$$\theta = \tan\text{-}1h/r$$

Powder X-ray diffraction studies:

X-ray powder diffraction (XRD) is a rapid analytical technique primarily used for phase identification of a crystalline material and can provide information on unit cell dimensions. The analyzed material is finely ground, homogenized and average bulk composition is determined. X-ray powder diffraction is most widely used for the identification of unknown crystalline materials (e.g. minerals, inorganic compounds).

Differential scanning calorimetry:

DSC is a thermo-analytical technique in which the differences in the amount of heat required to increase the temperature of a sample and reference are measured as a function of temperature. DSC can be used to measure a number of characteristic properties of a sample. Using this technique it is possible to observe fusion and crystallization events as well as glass transition temperatures. DSC can also be used to study oxidation, as well as other chemical reactions.

Fourier transforms infrared spectroscopy:

Fourier transform infrared spectroscopy (JASCO, FTIR-4100, Japan) spectra of the drug alone, solid dispersion and physical mixtures were observed. Approximately 1–2 mg of flupirtine, solid dispersion and physical mixtures were mixed with dry potassium bromide, and the samples were examined in a transmission mode over a wave number range of 4000 to 400 cm−1. Jasco spectramanager Ver. 2 (Japan) was used for data acquisition and analysis

RESULTS AND DISCUSSION

Then the solubility of the drug in distilled water was found in order to understand the extent to which the drug needs solubility enhancement. So, upon determination of solubility of drug through equilibrium method the solubility of drug in water was found to be 0.127%. The partition coefficient of the drug was also calculated using a mixture of water and octanol. The log of partition coefficient was found to be 3.2 indicating high hydrophobicity of the drug. Melting point of the drug was calculated through melting point apparatus. A small amount of the drug was added into a capillary tube that was blocked from side and an opening at the other that allowed the filling of the drug into capillary. Thermometer was placed to the adjacent of the capillary tube in order to note down the right temperature of melting. The drug powder started to melt at 174° C.

Standard curve of flupirtine maleate:

The UV spectrum of the drug in the range of 200-400nm on UV-visible spectrophotometer revealed that wavelength of maximum absorption (lambda max) of flupirtine was 304 nm.

Table 3: Standard plot data of flupirtine maleate

S. no.	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.188
3	20	0.386
4	30	0.599
5	40	0.880
6	50	0.996

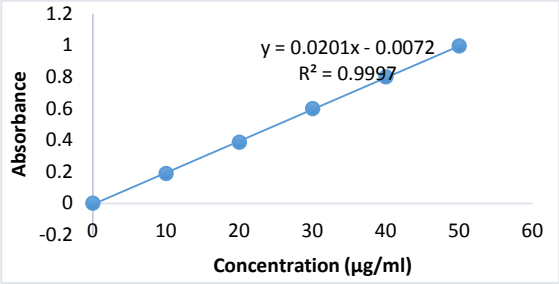


Figure 1: Calibration curve of flupirtine maleate

From the graph of absorbance vs. concentration for pure flupirtine it was observed that the drug obeysbeer's law in concentration range of 10-50 µg/ml (r= 0.999) at 304 nm (Table3, Figure 1).

Solubility studies of flupirtine maleate in difrrent hydrotropic solvent:

The solubility of the active pharmaceutical ingredients a key physicochemical factor impacting various junctures of drug discovery and development. A low aqueous solubility of a drug leads to poor therapeutic response. It plays a vital role in the design and development of different dosage forms for various routes of administration ranging from oral to parenteral. In the present case, the results of solubility studies for flupirtine in various hydrotropic agents are given in Table 4 & Fig. 2. The maximum solubility was found to be in a mixture of 20% niacinamide and Sodium benzoate. So this hydrotropic compound to be used in further studies.

Table 4: Results of solubility studies of flupirtine maleate in various aqueous solutions of solubilizers

S. No.	Blend	Blends composition (w/v)	Solubility (mg/ml)	% solubility
1	A	10%SB + 10%NM	128.22	12.82
2	B	10%NM + 10%FT + 10%SB	58.69	5.86
3	C	10%SB + 10%ST	50.69	5.06
5	E	20%NM+ 20%SB	163.86	16.38
6	F	20%SB+ 20%ST	140.02	14.00
7	G	20%FT+ 20%NM	150.96	15.09
8	H	10%NM+ 5% SB+ 5%ST+ 5%FT	58.72	5.87
9	I	20%SB+ 10%NM+ 10%SCI	130.20	13.02
10	J	15%SB+ 15%NM	109.79	10.97
11	K	10%SB+ 10%ST	60.96	6.09
12	L	10%NM+ 10%SCI+10%SA	72.78	7.27
13	M	5%NM+10%ST+5%FT	80.27	8.02
14	N	15%NM+5%SCI+10%FT	75.56	7.55
15	O	15%NM+15%ST	135.67	13.56

Where SB = Sodium benzoate, NM = Niacinamide, SCI = Sodium citrate, SA=sodiumacetate ST= PEG 6000, FT= PEG 4000

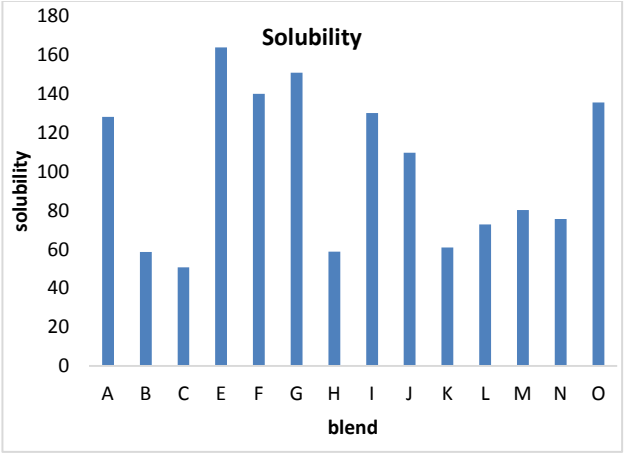


Figure 2: Graphical representation of solubility of flupirtine maleate in various aqueous solutions of solubilizers (blends)

Drug content:

Actual drug content of all five formulations were shown in (Table 5). The drug content of the prepared SDs was found to be in the range of 21.63 - 33.59 % indicating good uniformity in drug content in all the formulations.

Table 5: Estimation drug content of solid dispersions of flupirtine maleate

S.No.	Solid dispersion	Drug content (% w/v)
		Solid dispersion
1	SDA	21.63
2	SDB	23.86
3	SDC	25.63
4	SDD	33.59
5	SDE	24.67

Micromeritic studies:

Micromeritic properties of solid dispersion of a flupirtine maleate were studied by bulk density, tapped density, carr's index, hausner ratio and angle of repose. These studied are done to find out the particle size of the drugs that has been used in the formulation. The unit of particle size most frequently used in micromeritic is micrometer also known as micron. The studied were determined and shown in table 6

***In Vitro* dissolution studies:**

Dissolution studies were performed to compare the drug release from the solid dispersions, Physical mixtures to that of the pure drug. The dissolution test was carried out for a period of 60 min in water. All the experiments were carried out in duplicate and best result was found to be in SDB the results were shown in table 7. The drug release profiles were shown in figure 3.

Table 6: Results of micromeritic properties of solid dispersion SDA

S.No.	Parameter	Result
1	Bulk density (gm/cm^3)	0.491
2	Tapped density (gm/cm^3)	0.709
3	Compressibility index	19.26
4	Hausner ratio	1.045
5	Angle of repose	26.89

Table 7: Dissolution rate studies of solid dispersion SDB, physical mixture PMB and bulk drug flupirtine maleate

S.No.	Time (min)	SDB	PMB	Bulk drug
		% CDD	% CDD	% CDD
1	0	0	0	0
2	2	10.84	6.34	0.82
3	5	21.6	13.08	1.09
4	10	32.67	20.09	1.76
5	15	43.36	27.22	3.04
6	30	53.99	34.88	5.16
7	45	64.63	43.05	7.84
8	60	75.18	51.71	10.98
% CDD= % cumulative drug dissolved				

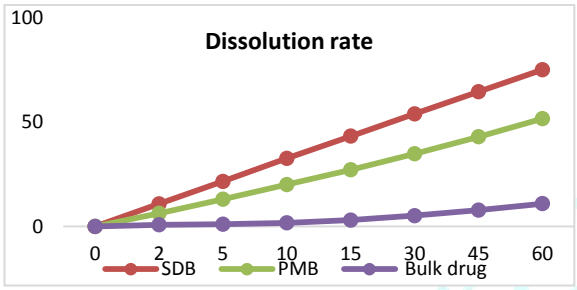


Figure 3: Cumulative % drug dissolved v/s time plot of solid dispersion SDB, physical mixture PMB and bulk drug flupirtine maleate

Flupirtine compatibility with excipients was studied by FTIR. The FTIR spectra of formulations with excipients reveal no interaction between drug and excipients; both the drug and excipients peaks were identified and interpreted in the spectra. The FTIR studies from the spectra confirmed the absence of any chemical interaction between the drug and excipients. The FT-IR spectra of drug and formulation are shown in figure 4.

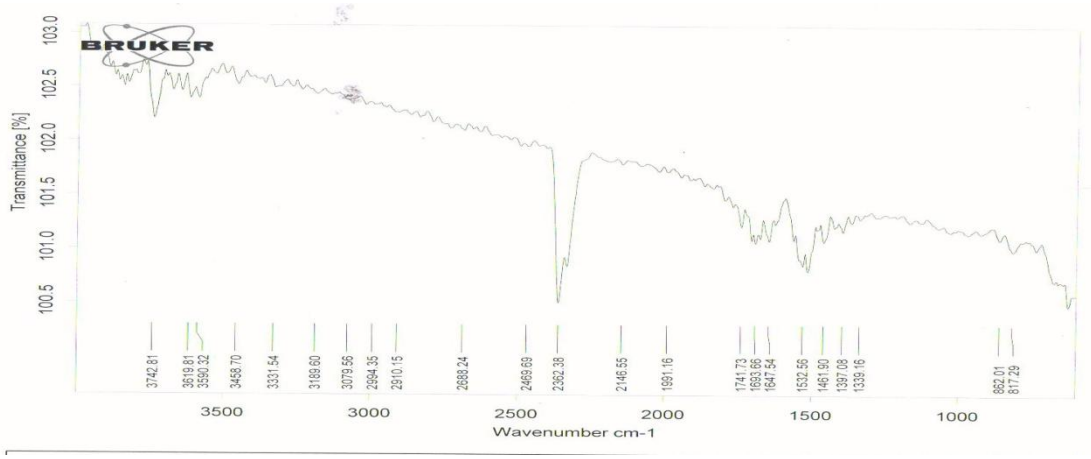
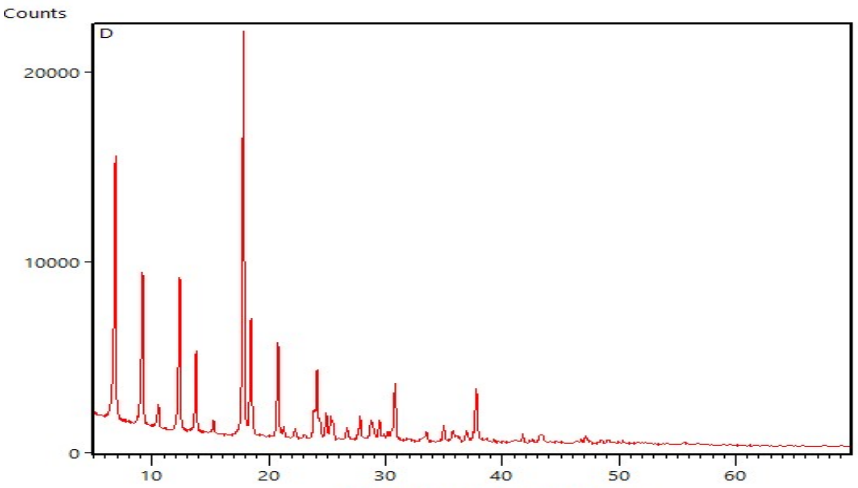
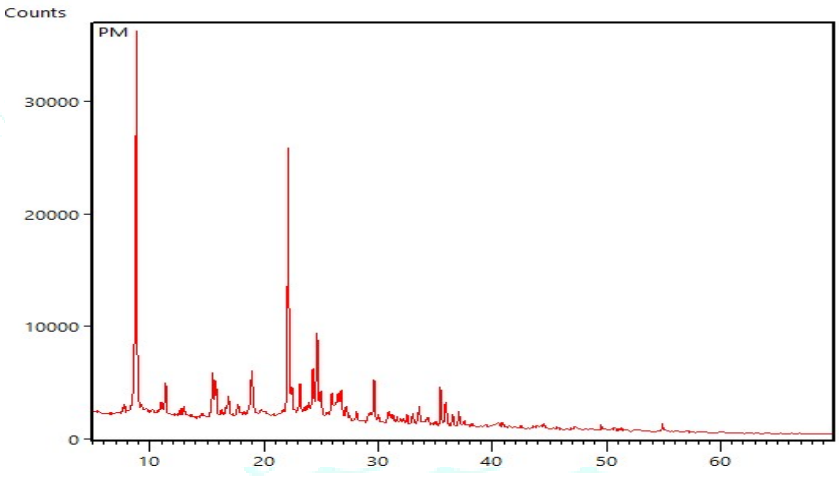


Figure 4: IR spectra of Solid dispersion (SDB)

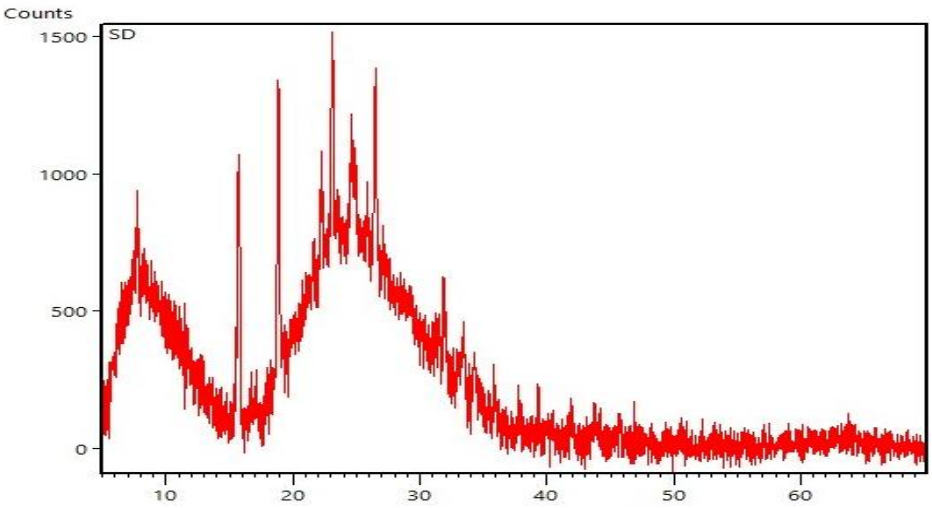
The X-ray diffraction pattern of flupirtine exhibited sharp, highly intense and less diffused peaks indicating the crystalline nature of drug as shown in figure 5(A). Optimized Formulations SDB revealed a reduction in peak intensity when compared with XRD of plain drug as shown in figure 5 (C). The characteristic peaks identified in the drug XRD was not detected in formulation. Decrease in the intensities and less number of peaks was probably due to change in crystal habit or conversion to an amorphous form. Reduced crystalline properties when compared to pure drug could account for increased dissolution.



(A)



(B)



(C)

Figure 5: XRD graph of (A) Pure drug (B) Physical mixture (PMB) (C) Solid dispersion (SDB)

DSC of the pure drug showed a sharp peak at 180ºC. DSC of SDB showed peak characteristic of the drug with no additional peaks. From DSC, it can be concluded that the drug and carrier showed no interaction. Thermo grams are shown in figure 6.

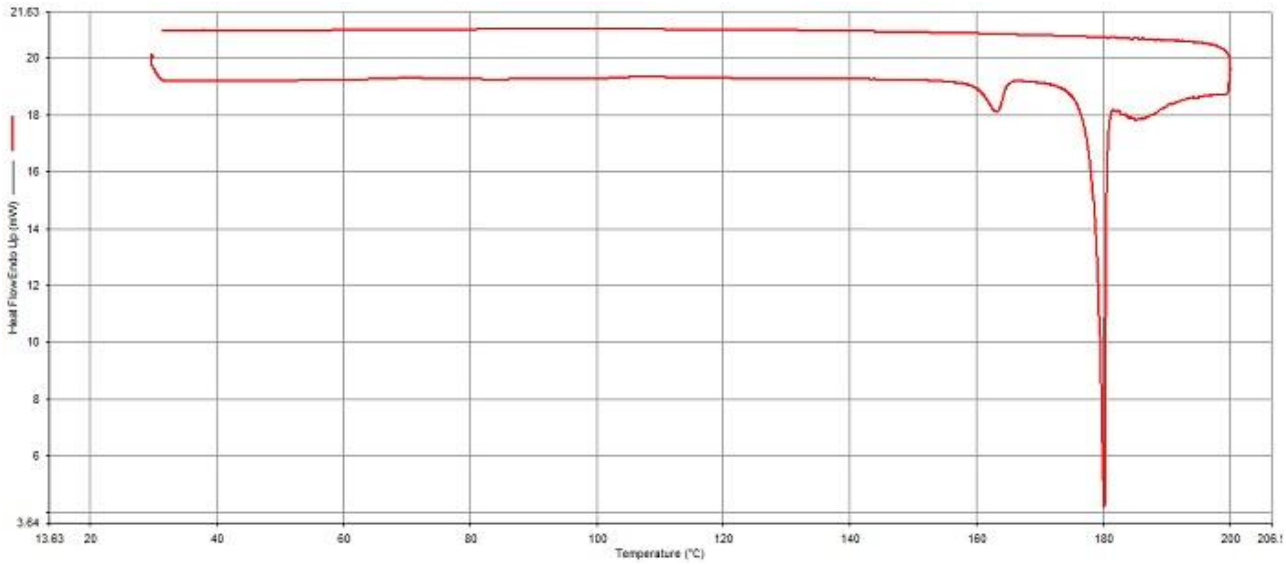


Figure 6: DSC graph of pure drug

CONCLUSION

The solid dispersions of flupirtine maleate were developed using the concept of mixed hydrotropic solubilization technique. Solid dispersions containing blend of niacinamide and sodium benzoate as water-soluble carriers show fast release of drug as compared with the pure bulk drug sample and PM; the quick onset of action and better extent of absorption is expected after oral administration of these HSDs. The proposed techniques would be economical, convenient and safe. Thus, the study opens the chances of preparing solid dispersion of poorly water-soluble drugs. If chemical stability of the drug remains unaffected to open a new era of more stable, economic and safe products in the market.

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Conflict of interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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