WORLD JOURNAL OF PHARMACY AND PHARMACEUTICAL SCIENCES

SJIF Impact Factor 7.421

Volume 8, Issue 1, 979-992 Research Article ISSN 2278 – 4357

FORMULATION AND EVALUATION OF PARACETAMOL SOLID DISPERSION TO ENHANCE THE SOLUBILITY AND DISSOLUTION CHARACTERISTICS

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Article Received on
02 Nov. 2018,

Revised on 23 Nov. 2018,
Accepted on 13 Dec. 2018

DOI: 10.20959/wjpps20191-12890

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ABSTRACT

Paracetamol is an analgesic and anti pyretic drug, used in treatment to relieve the pain and regulate the body temperature. The study was conducted to enhance the solubility of Paracetamol drug by Solid Dispersion technique by using Poly Ethylene Glycol 6000 (PEG 6000) and Hydroxy Propyl Methyl Cellulose (HPMC) as carriers. Three Drug: Carrier ratios (1:1, 1:2 and 1:3) were prepared by solvent evaporation, Physical mixture and Melting method. The prepared Solid Dispersions were evaluated for Estimation of drug content, FTIR study, Thermal studies, Aqueous solubility studies and Determination of Dissolution. Solid dispersion prepared by Solvent evaporation method using PEG 6000 at 1:3 drug : carrier ratio has shown highest improvement in the dissolution profile of Paracetamol. The carrier used and the techniques explored are relatively easy, simple, quick, inexpensive, and reproducible suggesting that solid dispersion is a trustworthy alternative for solubility enhancement of poorly water soluble drug.

KEYWORDS: Paracetamol, Solubility Enhancement, Solid Dispersion.

INTRODUCTION

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for showing pharmacological response. Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral

administration. Most of drugs are weakly acidic and weakly basic with poor aqueous solubility. 130 orally administered drugs on the WHO list, 61 could be classified with certainty. 84% of these belong to class I (highly soluble, highly permeable), 17% to class II (poorly soluble, highly permeable), 24(39%) to class III (highly soluble, poorly permeable) and 6 (10%) to class IV (poorly soluble, poorly permeable).[1] Drug release is an important and rate limiting step for oral bioavailability, particularly for drugs with low solubility and high permeability i.e. BCS class II drugs. By improving the drug release profile of BCS class II drugs, it is possible to enhance their bioavailability and reduce side effects.[2]

Numerous methodologies have been suggested and practically applied to improve the market ability of such drug candidates. These include the use of particle size manipulation via micronization and nanonization, use of complexing agents such as cyclodextrins, preparation of high energy drug states related to polymorphic or amorphic transformation, use of co-solvents, micellar solutions and lipid based systems for lipophilic drugs.[3]

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 or in crystalline particles .Therefore, based on their molecular arrangement, six different types of solid dispersions can be distinguished. Solid dispersions should preferably be designated according to their molecular arrangement.[4]

A pharmaceutical solid dispersion is an intimate mixture of a drug substance (solute) with diluents, termed a carrier (solvent or continuous phase). Solid dispersion systems in which the drug is dispersed in solid water-soluble matrices either molecularly or as fine particles have also shown promising result in increasing bioavailability of poorly water-soluble drugs.[5]

Advantages of solid dispersion

1. Preparation of solid dispersions results in particles with reduced particle size and thus the surface area is improved and increased dissolution rate is attained. The ultimate result is improved bioavailability.
2. Wettability is improved during solid dispersion production. Improved wettability results in increased solubility. Here the carriers play the major role to improve the wettability of the particles.

3. Particles in solid dispersions have been found to have a higher degree of porosity. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.
4. In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles

Disadvantages of Solid Dispersion

The major disadvantages of solid dispersion are related to their instability. Several systems have shown changes in crystalline and a decrease in dissolution rate with aging. The crystallization of Ritonavir from the supersaturated solution in a solid dispersion system was responsible for the withdrawal of the Ritonavir capsule (Norvir, Abboft) from the market. Moisture and temperature have more of a deteriorating effect on solid dispersions than on physical mixtures. Some solid dispersion may not lend them to easy handling because of tackiness.[6]

MATERIALS AND METHODS

Materials

Paracetamol, Polymers such as PEG 6000, HPMC are used. All reagents and solvent were of analytical grade and were used as received without further treatment.

Methods

Development of calibration curve for Paracetamol

a) The standard solutions for the drug having concentration 2, 4, 6, 8, 10, 12, 14, 16, 18 and 20 mg/ml was prepared with phosphate buffer pH 5.8.
b) From the stock solution. The absorbance of solutions of pure paracetamol drug were measured at 246 nm and a calibration curve was plotted between absorbance v/s concentration to get the linearity
c) Regression equation is shown in fig. 4.

Preparation of solid dispersions[7]

Solid dispersion of Paracetamol was prepared by melting and solvent evaporation method and physical mixtures. The composition is shown in table No:1.

Table 1: Composition of Solid Dispersion.

Formulation Code	Carrier	Drug : Carrier	Method
SD PEG SE 1 SD PEG SE 2 SD PEG SE 3	PEG 6000	1:1 1:2 1:3	Solid dispersion (solvent evaporation method)
SD HPMC SE 1 SD HPMC SE 2 SD HPMC SE 3	HPMC	1:1 1:2 1:3	Solid dispersion (solvent evaporation method)
SD PEG PM1 SD PEG PM2 SD PEG PM3	PEG 6000	1:1 1:2 1:3	Physical mixture
SD HPMC PM1 SD HPMC PM2 SD HPMC PM3	HPMC	1:1 1:2 1:3	Physical mixture
SD PEG1 SD PEG2 SD PEG3	PEG 6000	1:1 1:2 1:3	Solid dispersion (melting method)

Solvent Evaporation Method

In solvent evaporation method, the drug and carrier Poly Ethylene Glycol 6000 (PEG 6000) and Hydroxy Propyl Methyl Cellulose (HPMC) were mixed in 1:1, 1:2 and 1:3 ratios in ethanol separately. Solvent was removed by evaporation under reduced pressure. The mass was pulverised and passed through sieve # 100.

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 physical mixtures

For the sake of comparison, physical mixtures having the same composition of the solid dispersions were prepared by simply triturating the drugs and the polymers in a porcelain mortar. The mixtures were then sieved (420 µm) and stored in amber-glass capped containers.

EVALUATION OF PREPARED SOLID DISPERSION

Estimation of drug content: The formulation equivalent to 500 mg of drug was weighed and diluted suitably with distilled water. The absorbance was measured at 246 nm for the amount of drug in each formulation was calculated.

FTIR study[8]: For all the formulations and paracetamol the pellets have been prepared using potassium bromide (KBr) for FTIR study. The pellets were subjected to FTIR instrument 'Perkin Elmer FTIR spectrometer, spectrum 1000 Germany' for the collection of IR spectra which are illustrated in figures 2 to 7.

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.

Aqueous solubility studies[9]**:** It was carried out to determine solubility of drug alone in aqueous medium and also in presence of carriers like polyethylene glycol 6000 and Hydroxy Propyl Methyl Cellulose(HPMC). This was done by dissolving excess drug in different flasks containing different concentration of carrier in distilled water. The flasks were shaken thoroughly for 6 hours and kept aside for 24hours. The suspensions were filtered, diluted suitably and absorbance was measured at 246 nm for Paracetamol.

Determination of Dissolution[10]

Invitro release profiles for each batch was performed using USP dissolution apparatus (Electro lab, Mumbai, India). Solid dispersions of Paracetamol prepared by both the techniques was kept in the basket of dissolution apparatus and immersed in 900 ml distilled water at 37 ± 0.5° C and stirred at 100 rpm. Aliquot of 5 ml was withdrawn at time intervals of 15, 30, 45 and 60 min. The same amount of withdrawn volume was replaced with the dissolution medium in order to maintain the sink condition. The sample withdrawn was analyzed at 246 nm spectrophotometrically.

RESULTS AND DISCUSSION

Table 02: Development of Calibration Curve for Paracetamol.

λmax -246 nm

S.No.	CONCENTRATION (µg/ml)	ABSORBANCE At 246 nm
1.	0	0.000
2.	2	0.163
3.	4	0.356
4.	6	0.533
5.	8	0.727
6.	10	0.909
7.	12	1.127
8.	14	1.265

9.	16	1.46
10.	18	1.621
11.	20	1.803

r = 0.999

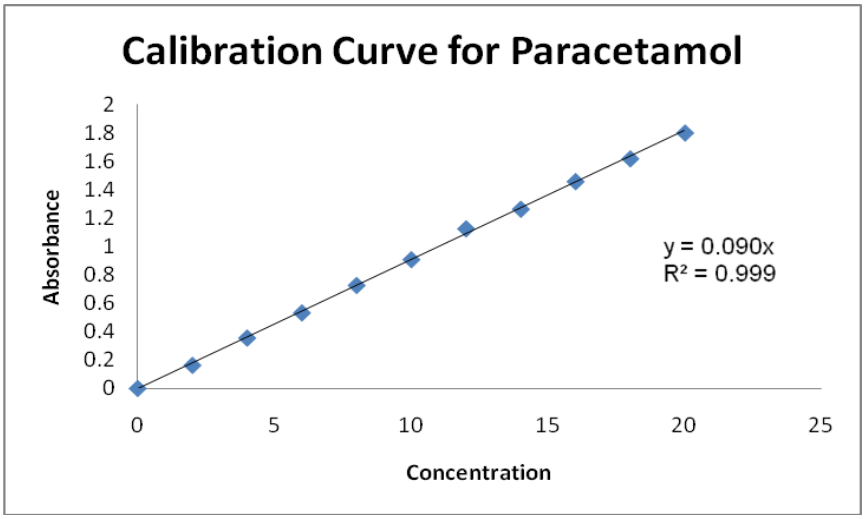

Figure 01: Calibration curve for Paracetamol.

ESTIMATION OF DRUG CONTENT

Table 03: Paracetamol PEG 6000 Solid Dispersion by solvent evaporation method.

SI NO	Formulation Code	Drug : Carrier (Ratio)	Drug content (%)
1	SD PEG SE 1	1:1	99.00%
2	SD PEG SE 2	1:2	99.76%
3	SD PEG SE 3	1:3	99.84%

Table 04: Paracetamol HPMC Solid Dispersion by solvent evaporation method.

SI NO	Formulation Code	Drug : Carrier (Ratio)	Drug content (%)
1	SD HPMC SE 1	1:1	93.41%
2	SD HPMC SE 2	1:2	93.24%
3	SD HPMC SE 3	1:3	93.05%

Table 05: Paracetamol PEG 6000 Solid Dispersion by Physical mixture method.

SI NO	Formulation Code	Drug : Carrier (Ratio)	Drug content (%)
1	SD PEG PM 1	1:1	99.22%
2	SD PEG PM 2	1:2	99.69%
3	SD PEG PM 3	1:3	99.78%

Table 06: Paracetamol HPMC Solid Dispersion by Physical mixture method.

SI NO	Formulation Code	Drug : Carrier (Ratio)	Drug content (%)
1	SD HPMC PM 1	1:1	93.80%
2	SD HPMC PM 2	1:2	93.60%
3	SD HPMC PM 3	1:3	93.37%

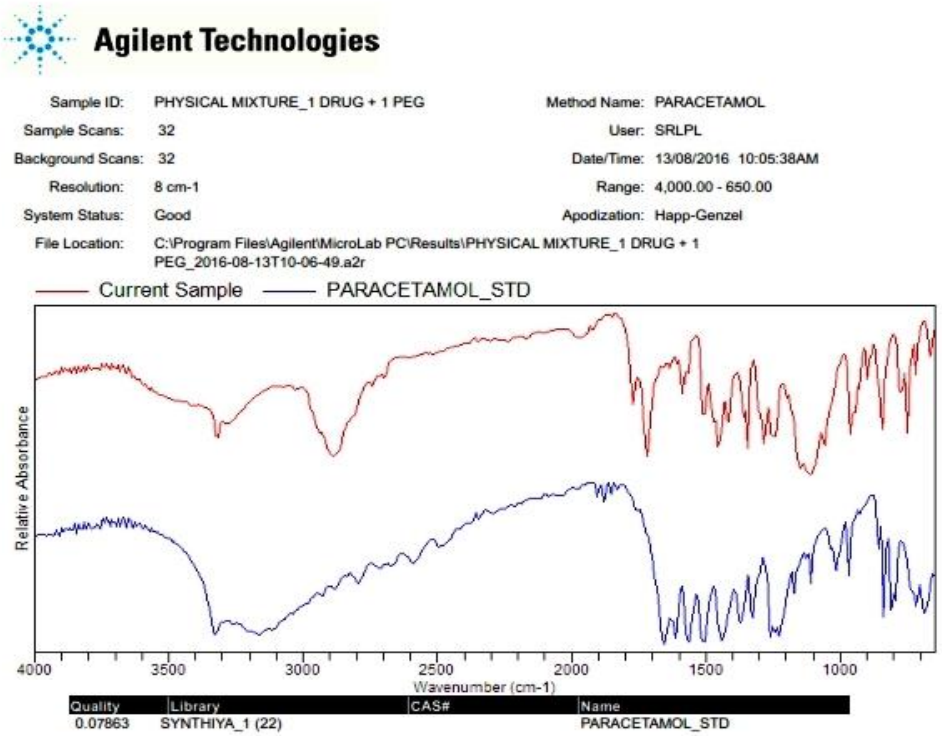

Figure 02: Physical Mixture 1Drug+1PEG.

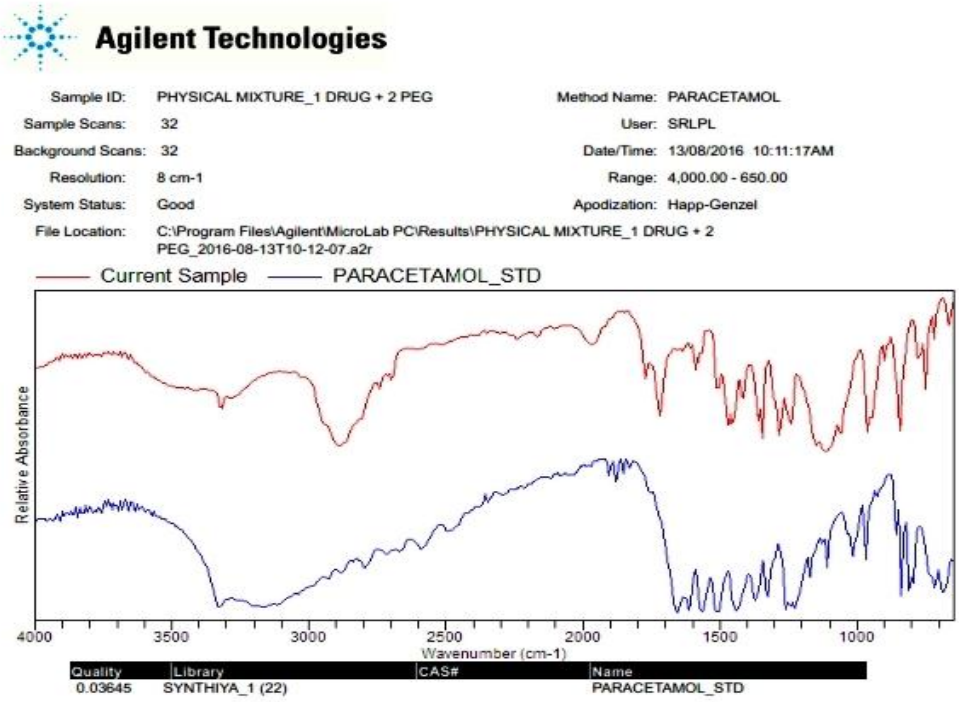

Figure 03: Physical Mixture 1Drug+2PEG.

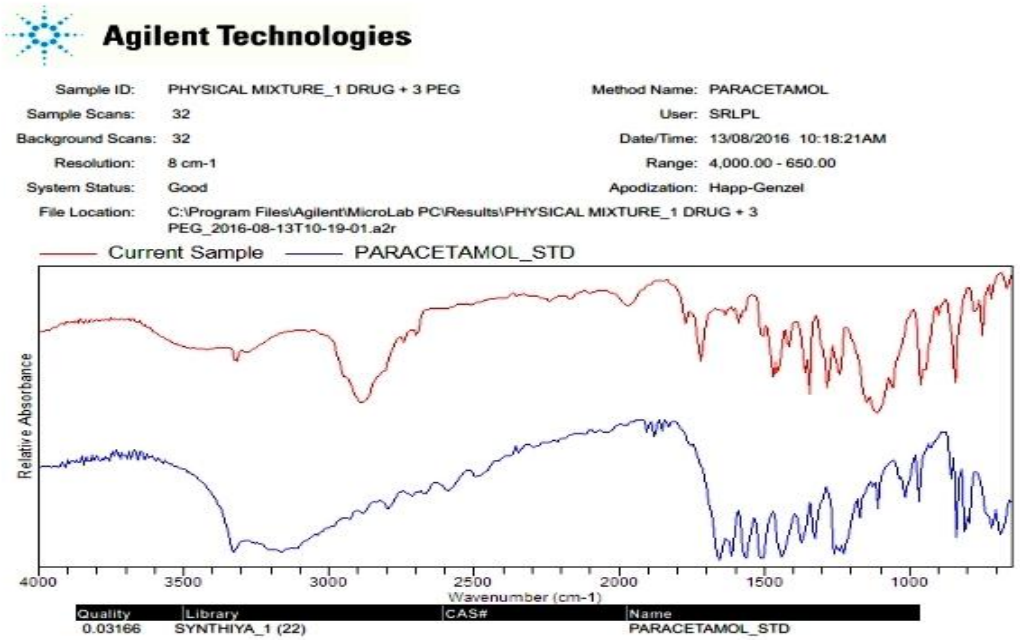

Figure 04: Physical Mixture 1Drug+3PEG.

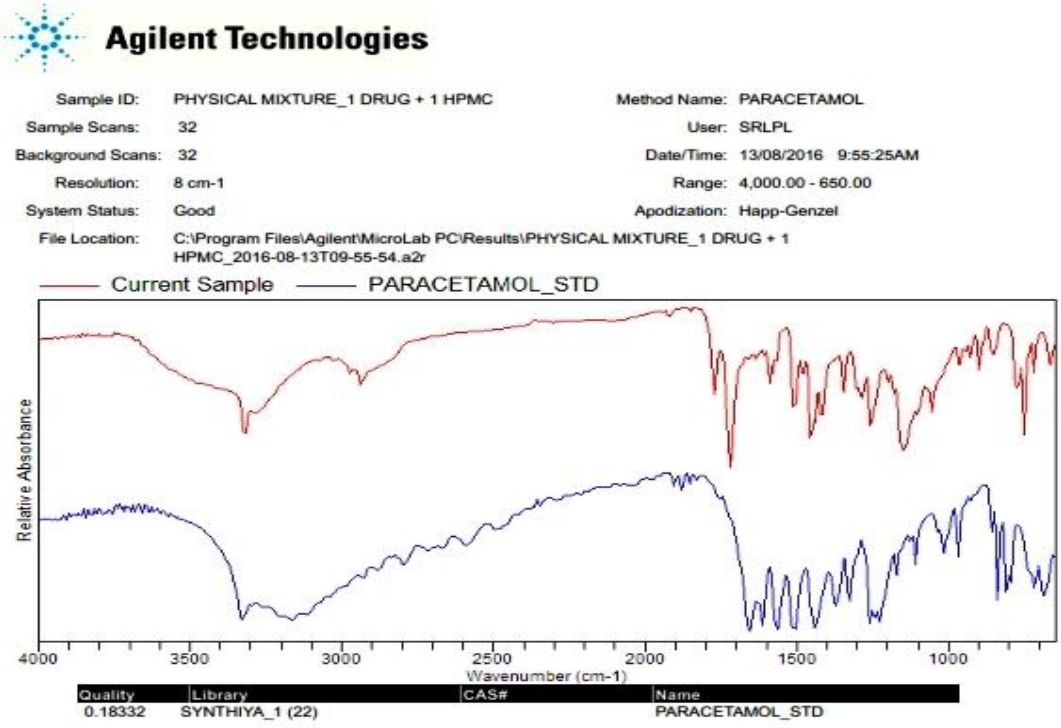

Figure 05: Physical Mixture 1Drug+1HPMC.

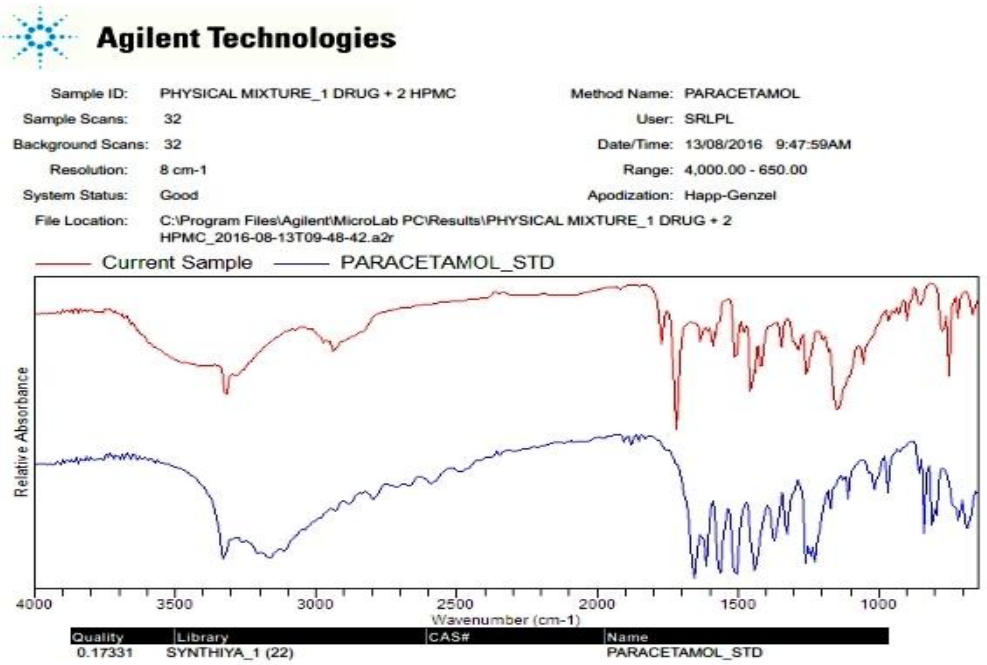

Figure 06: Physical Mixture 1Drug+2HPMC.

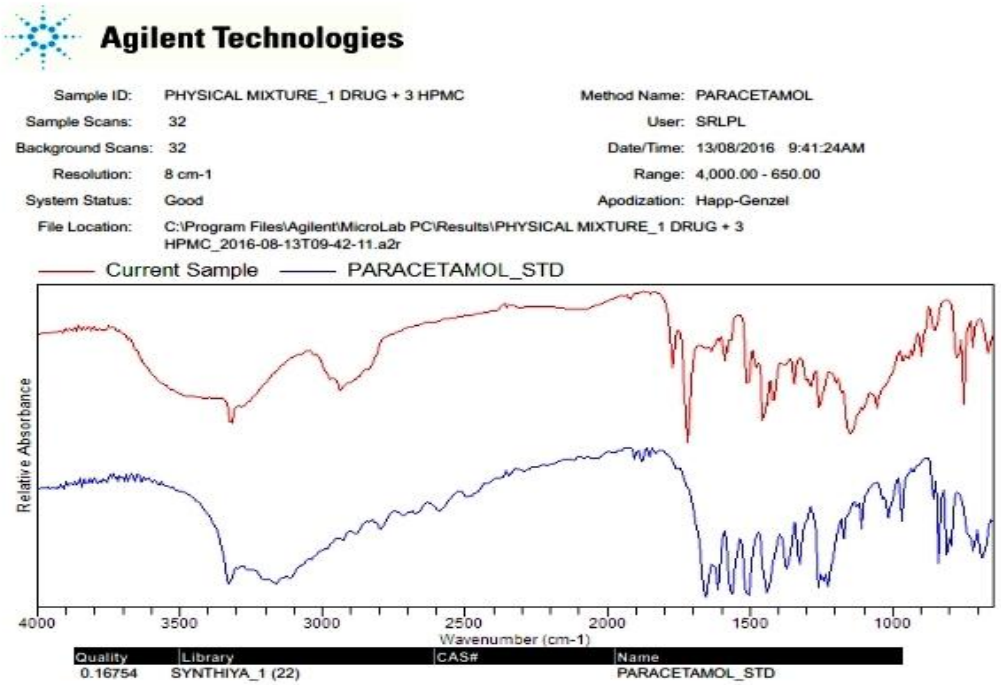

Figure 07: Physical Mixture 1Drug+3HPMC.

Thermal studies

Table 07: Paracetamol PEG 6000 Solid Dispersion by melting method.

SI NO	Drug Polymer Ratio Drug : PEG 6000	Melting Point of Paracetamol before Thermal Studies	Melting Point of Paracetamol after Thermal Studies
1	1:1	89°C	90°C
2	1:2	94°C	96°C
3	1:3	101°C	103°C

Table 08: Aqueous solubility studies.

SI NO	Formulation	Drug: Carrier Ratio	Solubility (mg/ml)
1	Paracetamol Pure Drug	-	0.092
2	Paracetamol PEG 6000 Solid Dispersion by solvent evaporation method	1:1	0.240
		1:2	0.281
		1:3	0.298
3	Paracetamol HPMC Solid Dispersion by solvent evaporation method	1:1	0.350
		1:2	0.381
		1:3	0.421
4	Paracetamol PEG 6000 Solid Dispersion by Physical mixture method	1:1	0.140
		1:2	0.196
		1:3	0.241
5	Paracetamol HPMC Solid Dispersion by Physical mixture method	1:1	0.180
		1:2	0.212
		1:3	0.260

Dissolution Studies

***IN VITRO* RELEASE STUDY**

Table 09: *In vitro* release profile of Paracetamol Solid Dispersions in PEG 6000.

S.No	Time (Mins)	Pure Drug	Formulation Code SD PEG PM			Formulation code SD PEG SE		
			1:1	1:2	1:3	1:1	1:2	1:3
1	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2	15	10.22%	32.87%	34.38%	45.51%	35.26%	50.03%	60.22%
3	30	33.13%	40.27%	47.30%	52.38%	45.30%	61.83%	69.57%
4	45	47.65%	54.66%	62.58%	68.27%	73.63%	76.63%	83.80%
5	60	60.11%	81.34%	82.30%	87.73%	85.27%	87.61%	89.41%

Table 10: *In vitro* release profile of Paracetamol Solid Dispersions in HPMC

S.No	Time (Mins)	Pure Drug	Formulation Code SD HPMC PM			Formulation code SD HPMC SE		
			1:1	1:2	1:3	1:1	1:2	1:3
1	0	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%	0.0%
2	15	10.22%	13.52%	16.04%	26.75%	9.15%	11.12%	20.78%
3	30	33.13%	22.54%	25.83%	30.73%	12.52%	21.66%	32.72%
4	45	47.65%	31.62%	40.84%	47.51%	17.72%	29.93%	40.61%
5	60	60.11%	54.36%	61.60%	69.39%	32.71%	41.05%	61.11.%

DISCUSSION

Calibration curve for Paracetamol

Calibration curve for Paracetamol was developed in Phosphate buffer pH-5.8 using UV spectrophotometer and the results are given in Table 02 and figure 01. The λmax was found to be 246 nm for Paracetamol, at which the absorbances of standard solutions (0-20µg/ml) were measured. Calibration between the concentration and absorbance were developed with a regression co-efficient of 0.999, which showed linearity between 0-20µg/ml ranges for Paracetamol.

Compatibility Studies

Compatibility of Paracetamol PEG 600 and HPMC were studied by FTIR spectral matching approach. The respective spectra are given in figures 02 ,03, 04, 05, 06 and 07. By comparing the spectra, it was concluded that there was no significant change in spectral pattern of physical mixtures of drug and polymer, which confirmed the compatibility of Paracetamol with the polymers. The Principal peaks obtained in IR spectra of samples were almost similar to that of pure drug, indicating no interaction between drug and polymers.

Estimation of drug content

The estimation of drug (Paracetamol) in the prepared Paracetamol Solid Dispersions are given in Table 03, 04, 05 and 06**.** In Paracetamol: PEG 6000 Solid Dispersion prepared by solvent evaporation method, the formulation code SD PEG SE 1 has the least Drug content of 99.00%, whereas the formulation code SD PEG SE 3 has the least Drug content of 99.84% is shown in table 03.

In Paracetamol: HPMC Solid Dispersion prepared by solvent evaporation method, the formulation code SD HPMC SE 3 has the least Drug content of 93.05%, whereas the formulation code SD HPMC SE 1 has the least Drug content of 93.41% is shown in table 04.

In Paracetamol: PEG 6000 Solid Dispersion prepared by Physical mixture method, the formulation code SD PEG PM 1 has the least Drug content of 99.22%, whereas the formulation code SD PEG PM 3 has the least Drug content of 99.78% is shown in table 05.

In Paracetamol: HPMC Solid Dispersion prepared by Physical mixture method, the formulation code SD HPMC PM 3 has the least Drug content of 93.37%, whereas the formulation code SD HPMC PM 1 has the least Drug content of 93.80% is shown in table 06.

Thermal studies

The results of thermal studies of Paracetamol PEG 6000 Solid Dispersion prepared by melting method are shown in table 07. The melting point of paracetamol PEG 6000 Solid Dispersion before thermal studies were found to be 89°C, 94°C and 101°C for 1:1, 1:2 and 1:3 respectively. Whereas the melting point of paracetamol PEG 6000 Solid Dispersion after thermal studies were found to be 90°C, 96°C and 103°C and 101°C for 1:1, 1:2 and 1:3 respectively.

Aqueous solubility studies

The results of aqueous solubility studies are shown in table 08. The solubility of Paracetamol PEG 6000 Solid Dispersion by solvent evaporation method was found to be 0.240, 0.281 and 0.298 mg/ml for 1:1, 1:2 and 1:3 respectively. The solubility of Paracetamol HPMC Solid Dispersion by solvent evaporation method was found to be 0.350, 0.381 and 0.421 mg/ml for 1:1, 1:2 and 1:3 respectively.

The solubility of Paracetamol PEG 6000 Solid Dispersion by Physical mixture method was found to be 0.140, 0.196 and 0.241 mg/ml for 1:1, 1:2 and 1:3 respectively. The solubility of Paracetamol HPMC Solid Dispersion by Physical mixture method was found to be 0.180, 0.212 and 0.260 mg/ml for 1:1, 1:2 and 1:3 respectively. The solubility for pure drug was found to be 0.092 mg/ml.

***In vitro* release study**

The In vitro release profile of Paracetamol Solid Dispersions in PEG 6000 is given in table 09. The drug release at the end of 60 minutes for Formulation Code SD PEG PM were found to be 60.11%, 81.34%, 82.30% and 87.73% for Pure Drug, 1:1, 1:2 and 1:3 ratios respectively. For Formulation Code SD PEG SE were found to be 60.11%, 85.27%, 87.61% and 89.41% for Pure Drug, 1:1, 1:2 and 1:3 ratios respectively.

The In vitro release profile of Paracetamol Solid Dispersions in HPMC is given in table 10. The drug release at the end of 60 minutes for Formulation Code SD HPMC PM were found to be 60.11%, 54.36%, 61.60% and 69.39% for Pure Drug, 1:1, 1:2 and 1:3 ratios respectively. For Formulation Code SD HPMC SE were found to be 60.11%, 32.71%, 41.05%, 61.11.%for Pure Drug, 1:1, 1:2 and 1:3 ratios respectively.

SUMMARY AND CONCLUSION

Paracetamol is an analgesic and anti pyretic drug used in treatment to relieve the pain and regulate the body temperature. The solubility and dissolution profile of Paracetamol, a poorly water soluble drug, was significantly improved by preparing solid dispersion with water soluble carriers like PEG 6000 and HPMC by solvent evaporation technique, Physical mixture and Melting method. Thermal studies prove that the increase in drug polymer concentration increases the melting point. From the Aqueous solubility studies it is evident that the solubility of Paracetamol has been increased as the polymer concentration increases. Solid dispersion prepared by Solvent evaporation method using PEG 6000 at 1:3 drug : carrier ratio has shown highest improvement in the dissolution profile of Paracetamol. The carrier used and the techniques explored are relatively easy, simple, quick, inexpensive, and reproducible suggesting that solid dispersion is a trustworthy alternative for solubility enhancement of poorly water soluble drug.

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