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PREPARATION AND EVALUATION OF SOLID DISPERSIONS OF NIMESULIDE

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ABSTRACT

Nimesulide is a non-steroidal anti-inflammatory drug. Here, the present study was planned to prepare and evaluate the solid dispersions of Nimesulide. Solid dispersions of Nimesulide were prepared by using various hydrophilic carriers like PVP K-40, PEG 4000, PEG-6000 in various ratios by solvent evaporation method. The solubility of Nimesulide in different solvents; water, acetone and ethanol was enhanced in the form of solid dispersions. The prepared solid dispersions were subjected to solubility studies (in water, 0.1 N HCL and phosphate buffer pH 7.4. Stability studies were carried out at 40±2° C and at 75±5 % RH. The phosphate buffer pH 7 Showed highest solubility for the drug. The cumulative amount of drug release of Nimesulide: PVP K-40 was 97.06 %; Nimesulide: PEG-4000 was 97.42%; Nimesulide: PEG -6000 was 97.46% respectively. Therefore it can be concluded that dissolution rate of poorly soluble drug (Nimesulide) can be significantly enhanced by formulating them into solid dispersions

Keywords: Nimesulide, PVP K-40, PEG-4000, PEG – 6000, Solubility.

INTRODUCTION

The solubility behaviour of drug is a key determinant of its oral bioavailability. With the recent advent of high throughput screening of potential therapeutic agents, the number of poorly soluble drug candidates has sharply and the formulation of poorly soluble compounds for oral delivery now presents one of the most frequent and greatest challenges to formulation scientists in pharmaceutical industry.

The dissolution rate is directly proportional to saturation of drug. Therefore aqueous solubility of a drug can be used as first approximation of its dissolution rate. Drugs with low aqueous solubility have low dissolution rates and hence suffer from oral bioavailability problems. Solid dispersions seem to be a viable technique for overcoming this problem.[6,7]

Solid dispersion is defined as dispersions of one or more active ingredients in an inert carrier or matrix at solid state prepared by fusion method, hot melt extrusion method, solvent evaporation method and spray drying technique [8]. Of all the above techniques solvent evaporation technique is feasible for manufacturing processes.

It is a unique approach to present a poorly soluble drug in an extremely fine state of subdivision in gastrointestinal fluids. Various carriers have been used in the formation of solid dispersion, which can facilitate in improving the dissolution rate of poorly soluble drugs to improve better bioavailability. The two most used matrices, PEG and PVP, have very good binding properties. Moreover, they fill up the pores during the compaction process thereby hindering rapid dissolution of the tablet. [2]

Solvent evaporation method: In this method, physical mixture of two components are dissolved in a common solvent and followed by the evaporation of solvent. This method has been used for long time in the preparation of solid solution or mixed crystal of organic or inorganic compounds. The advantages of this method are low temperature requirement for

the preparation of dispersion and thermal decomposition of drugs and carriers can be prevented.[1]

MATERIALS AND METHODS

The materials and sources used in our study are presented in **Table** 1**.**

Preparation of solid dispersions: Solid dispersions can be produced from hydrophilic polymers (like PVP K-40, PEG-4000, and PEG-6000) by the following methods and using the process variables like drug : polymer ratio.

Solvent Evaporation Method: Solid dispersions of Nimesulide were prepared using PVP K-40, PEG-4000 and PEG-6000 in the ratios 1:1, 1:4, 1:9 individually by solvent evaporation method. Nimesulide and water soluble carriers in different ratios were accurately weighed and transferred to a beaker containing ethanol.

Then solvent was evaporated in vacuum evaporator and the resulting solid dispersion were stored in desiccators until solid dispersions attain constant weight, the solidified masses were crushed, pulverized and passed through mesh number 40.[4,5]

Formulation of solid dispersions with changing drug: polymer ratio: Three different formulations namely F1, F2 and F3 were formulated taking 100 mg of the drug and three different polymers with varying polymer concentrations of 100 mg, 400 mg and 900 mg respectively as given in the **Table 2.**

Percentage drug content study: Drug content was determined by dissolving solid dispersion equivalent to 10 mg of drug in 0.1 N methanolic HCl kept in ultrasonicator for 20 min. Volume was adjusted to 100 ml. Then, tablet solution was filtered through Whatman filter paper No. 41. Solution was suitably diluted and absorbance was measured at 393 nm using double beam UV spectrophotometer.

10 mg of drug--------→ 0.1 Methanolic HCl -------→ Ultrasonicator (20 min) -------→ Volume was adjusted to 100 ml--------→ filtered through Whatman filter paper n. 41-----→ suitably diluted-----→ absorbance was measured at 393 nm using double beam spectrophotometer.

Solubility studies: Solubility study was performed according to method reported by Higuchi and Connors. Excess of solid dispersions were added to 25 ml distilled water, 0.1 N HCl, Phosphate buffer of Ph 7.4 taken in a stoppered conical flask and mixture were shaken for 24 hrs in a rotary flask shaker. [4]

Dissolution study/ in-vitro release: Solid dispersions equivalent to 10 mg of Nimesulide was filled in hard gelatin capsule by hand filling method. Dissolution study was carried out using USP XXI six station dissolution test apparatus employing USP Type I apparatus. Dissolution study was carried out in a 900 ml of pH 7.4 phosphate buffer at 37±0.5°C at 100 rpm. 10 ml samples were withdrawn at time intervals of 5, 10, 15, 20, 25, 30, 45, 60, 75 and 90 min. The volume of dissolution medium was adjusted to 900 ml by replacing each 10 ml aliquot withdrawn with 10 ml of fresh pH 7.4 phosphate buffer.

The concentration of Nimesulide in samples was determined at each time by measuring absorbance at 393 nm. Cumulative percent drug released was determined at each time interval. Pure Nimesulide was used as control, t_{90} of various dispersions was calculated, t_{90} is the time required for 90% dissolution of drug.

Stability studies: The solid dispersions of Nimesulide were stored at 40±2°c and at 75±5% RH for a period of 45 days. At weekly intervals, 5 ml of sample was withdrawn and analyzed for the drug content. They were also observed for any physical changes during the period of storage.

Standard calibration curve of Nimesulide: Standard calibration curve was spectro photometrically determined for Nimesulide in two different media that is DMF and a mixture of 70: 30 of methanol: water, at respective λ_{max} for the estimation of drug content and for the estimation of drug in the *in vitro* dissolution studies. 125 mg accurately weighed quantity of drug was dissolved in 500 ml DMF. Further 2 ml of this solution was diluted to 50 ml with DMF to obtain a stock solution. Aliquots were suitably diluted.

The spectrophotometric absorption for a series of concentrations was determined at 436 nm λ_{max} in DMF, against DMF as blank. Similarly for calibration curve of Nimesulide in mixture solvent of 70: 30 ratio of methanol: water. Accurately weighed 100 mg of drug was dissolved in 100 ml of the mixture solvent. From this 1 ml was diluted to 100 ml. Further sample aliquots were withdrawn and suitably diluted with the solvent. Absorption at λ_{max} was noted against mixture solvent as blank for various concentrations of the drug at 304 λ_{max}.

RESULTS

Solubility enhancement of solid dispersions: The solubility of Nimesulide in different solvents was found to be enhanced in solid dispersions of PVP K-40[10,11], PEG 4000 and PEG 6000 (**Table 3)**

Percentage drug content study: The percentage drug content study for different formulations are presented in (**Table 4)**

Standard calibration curve of Nimesulide: The calibration curves plotted in both cases were found to almost pass through the origin. From the calibration curve it was found that Nimesulide in DMF was found to obey Beer-Lambert's law in the concentration range of 0 -14 µg/ml. standard calibration curve of nimesulide spectrometrically in DMF and methanol: water system are shown in **Table 5** and **Figure 1.**

Dissolution study curves: The dissolution curve readings & figure for **F1 a** [1:1] are presented in **(Table 6**), **Figure (2)**
The dissolution curve readings & figure for **F1 b** [1:4] are presented in **(Table 7), Figure (3)**
The dissolution curve readings & figure for **F1 c** [1:9] are presented in **(Table 8), Figure (4)**
The dissolution curve readings & figure for **F2 a** [1:1] are presented in **(Table 9), Figure (5)**
The dissolution curve readings & figure for **F2 b** [1:4] are presented in **(Table 10), Figure (6)**
The dissolution curve readings & figure for **F2 c** [1:9] are presented in **(Table 11), Figure (7)**
The dissolution curve readings & figure for **F3 a** [1:1] are presented in **(Table 12), Figure (8)**
The dissolution curve readings & figure for **F3 b** [1:4] are presented in **(Table 13), Figure (9)**
The dissolution curve readings & figure for **F3c** [1:9] are presented in **(Table 14), Figure (10)**

Stability study: The stability study results are depicted in **Table 15**

DISCUSSION

In the present study, solid dispersions of Nimesulide could be successfully prepared by solvent evaporation method. Among the various methods reported for preparation of solid dispersions, this method was chosen as it is simple and novel method which is feasible in the industry.

The method of estimation of Nimesulide by UV spectrophotometer at respective wavelengths was standardized and drug was found to obey Beer-Lambert's law in the concentration range of 0-14 µg/ml. Percentage drug content was determined by dissolving solid dispersion equivalent to 10 mg of drug in 0.1 N Methanolic HCl. It showed a range of 96.62 to 97.92 %. This showed the uniform distribution of drug in all solid dispersions.

The prepared solid dispersions were subjected to solubility studies in distilled water, 0.1 N HCl and phosphate buffer pH 7.4. The phosphate buffer pH 7.4 showed highest solubility for the drug. All solid dispersions showed enhancement in the solubility as compared to pure drug alone. The drug: carrier ratio (1:9) showed higher solubility as compared to other ratios. The ratio of 1:9 showed higher solubility may be due to higher proportion of hydrophilic carriers present in solid dispersions.[3]

As soluble carrier dissolves, the insoluble drug gets exposed to aqueous environment as very fine particles and solubility gets increased. Enhancement in solubility was observed in following order. PVP K-40> PEG 6000> PEG 4000. The rapid dissolution of Nimesulide from solid dispersion may be attributed to molecular and colloidal dispersion of drug in hydrophilic carrier matrix. The drug: carrier ratio (1:9) showed faster dissolution as compared to other ration due to increased proportion of water soluble carriers in solid dispersions.[9,10] As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution. Dissolution profile of Nimesulide was fast from Nimesulide: PVP K-40. Stability studies were carried out at 40±2° C and at 75±5 % RH for a period of 45 days and the formulation did not show any physical change and neither there was any significant change in drug content.

CONCLUSION

Solid dispersions of Nimesulide could be successfully prepared by solvent evaporation and fusion method using various water soluble carriers such as polyvinyl pyrrolidone (PVP K-40), polyethylene glycol 4000 (PEG 4000), and polyethylene glycol 6000 (PEG 6000). The solubility of Nimesulide in different solvents; water, acetone and ethanol was enhanced in the form of solid dispersions. All solid dispersions showed enhancement in the solubility as compared to pure drug alone. The drug: carrier ratio (1:9) of all the water soluble carriers showed higher solubility as compared to 1:1 and 1:4 in all solid dispersions. The phosphate buffer (pH 7.4) showed highest solubility for the drug. Percentage drug content was found to be

in the range of 96.62 and 97.92. It shows uniform distribution of drug in all solid dispersions. The cumulative percent of drug release of Nimesulide: PVP K-40 showed 97.06 %; Nimesulide: PEG 4000 showed 97.42 %; Nimesulide: PEG 6000 showed 97.46 % drug release respectively. The formulations were stable at 40±2 °C and at 75±5 % RH. Therefore it can be concluded that the formulation of solid dispersions of Nimesulide helped to significantly increase the solubility and dissolution of the drug using various hydrophilic carriers.

Table 1: Materials, Instruments and sources

Materials &instruments	Sources
Nimesulide	Apex Drugs & Intermediates Ltd. Hyderabad, India
PVP K-40	S.D. Fine Chemicals Ltd., Mumbai
PEG – 4000	S.D. Fine Chemicals Ltd., Mumbai
PEG- 6000	S.D. Fine Chemicals Ltd., Mumbai
Methanolic HCL	Loba Chemicals Ltd., Mumbai
Ethanol	S.D. Fine Chemicals Ltd., Mumbai
Ultrasonicator	M/s Enertech Electronics Pvt. Ltd.
Double beam UV spectrophotometer	M/s Shimadzu (UV-1601)
Rotary flask shaker	M/s Remi Equipments (P) Ltd., Mumbai
Dissolution test apparatus	M/s Enertech Electronics Pvt. Ltd.

Table 2: Formulation of solid dispersions with changing drug: polymer ratio

Formulation code	Drug: polymer ratio
F1a	1:1
F1b	1:4
F1c	1:9
F2a	1:1
F2b	1:4
F2c	1:9
F3a	1:1
F3b	1:4
F3c	1:9

Table 3: Solubility enhancement of solid dispersions

Solvent	Pure Nimesulide	Solid dispersions
Water	Insoluble	Slightly soluble
Ethanol	Slightly soluble	freely soluble
Acetone	Soluble	freely soluble

Table 4: Percentage drug content study

System	Percentage drug content
F1a	96.62%
F1b	97.92%
F1c	96.86%
F2a	97.82%
F2b	97.40%
F2c	97.06%
F3a	97.78%
F3b	97.28%
F3c	97.32%

Table 5 -Standard calibration curve readings of Nimesulide spectrometrically in DMF & Methanol:Water

DMF

Concentration in µg/ml	Absorbance
0	0.0000
2	0.1490
4	0.3030
6	0.4253
8	0.5666
10	0.7300

Methanol:Water

Concentration in µg	Absorbance
5	0.132
10	0.231
15	0.350
20	0.472
25	0.583
30	0.711
35	0.821
40	0.942

Table: 6
Dissolution curve readings F1a(1:1)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.5	0.033
2	10	0.9	0.064
3	20	2.0	0.146
4	30	2.8	0.190
5	40	3.1	0.210
6	50	4.2	0.300
7	60	5.1	0.346
8	70	6.0	0.410
9	80	6.6	0.456
10	90	7.1	0.499

Table:7
Dissolution curve readings F1b(1:4)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.6	0.034
2	10	0.8	0.062
3	20	2.1	0.149
4	30	2.9	0.192
5	40	3.3	0.221
6	50	4.1	0.299
7	60	5.0	0.346
8	70	6.1	0.412
9	80	6.7	0.457
10	90	7.2	0.510

Table:8
Dissolution curve readings F1c(1:9)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.6	0.034
2	10	0.9	0.064
3	20	2.2	0.152
4	30	2.9	0.192
5	40	3.4	0.230
6	50	4.2	0.300
7	60	5.1	0.350
8	70	6.2	0.418
9	80	6.8	0.460
10	90	7.3	0.515

Table: 9
Dissolution curve readings F2a(1:1)

S.No.	**Time**	**Conc. (µg/ml)**	**Abs**
1	5	0.3	0.016
2	10	0.4	0.031
3	20	0.9	0.064
4	30	1.6	0.100
5	40	2.0	0.145
6	50	3.0	0.194
7	60	4.1	0.299
8	70	5.0	0.348
9	80	6.0	0.410
10	90	7.0	0.498

Table: 10
Dissolution curve readings F2b(1:4)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.4	0.031
2	10	0.7	0.053
3	20	1.7	0.110
4	30	2.6	0.180
5	40	3.2	0.200
6	50	3.7	0.270
7	60	4.3	0.310
8	70	5.2	0.350
9	80	6.6	0.460
10	90	7.2	0.510

Table:11
Dissolution curve readings F2c(1:9)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.6	0.048
2	10	1.1	0.089
3	20	1.9	0.120
4	30	2.8	0.190
5	40	3.5	0.250
6	50	3.9	0.285
7	60	4.5	0.325
8	70	5.5	0.365
9	80	6.8	0.475
10	90	7.5	0.600

Table :12
Dissolution curve readings F3a (1:1)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.4	0.030
2	10	0.6	0.049
3	20	1.1	0.088
4	30	2.0	0.115
5	40	2.5	0.175
6	50	3.2	0.205
7	60	3.8	0.280
8	70	4.4	0.324
9	80	6.0	0.400
10	90	7.2	0.500

Table:13
Dissolution curve readings F3b (1:4)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.4	0.030
2	10	0.6	0.049
3	20	1.2	0.089
4	30	2.1	0.120
5	40	2.7	0.180
6	50	3.3	0.210
7	60	3.9	0.285
8	70	4.6	0.330
9	80	6.2	0.415
10	90	7.4	0.510

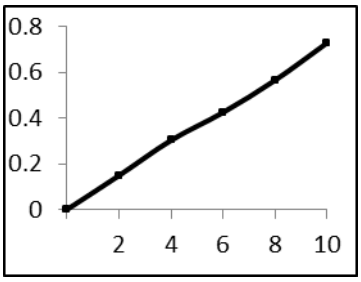
Table:14 -Dissolution curve readings F3c (1:9)

S.No.	Time	Conc. (µg/ml)	Abs
1	5	0.6	0.049
2	10	1.0	0.085
3	20	1.9	0.120
4	30	3.0	0.194
5	40	3.6	0.250
6	50	4.1	0.290
7	60	5.3	0.350
8	70	6.4	0.430
9	80	6.8	0.495
10	90	7.5	0.520

Table:15 - Stability study results

FORMULATION CODE	TEMP	PHYSICAL STABILITY NO. OF WEEKS 0	2	4	6	DRUG CONTENT (%) NO. OF WEEKS 0	2	4	6
F1c	40°C	No change in physical appearance				100	97	86	76
F2c		No change in physical appearance				100	98	87	75
F3c		No change in physical appearance				100	97	86	77

DMF



Methanol: water

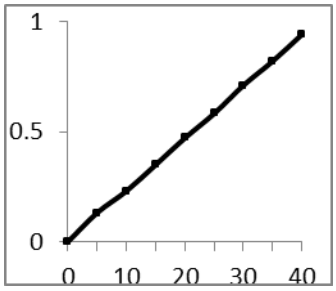


Fig : 1 -Standard calibration curve of Nimesulide spectrometrically in DMF & Methanol: water system

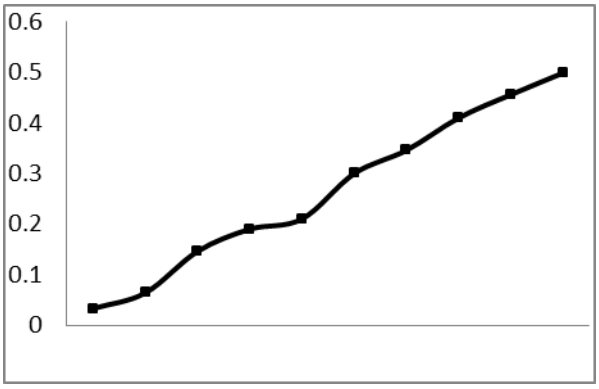


Fig:2 -Dissolution curve of F1a (1:1)

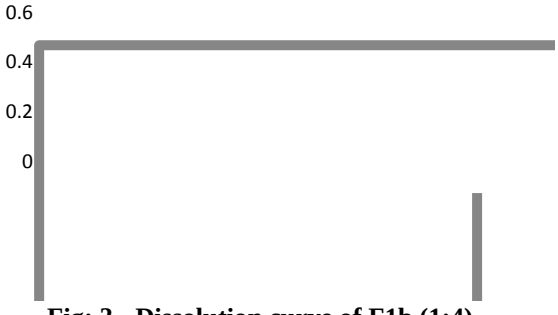


Fig: 3 - Dissolution curve of F1b (1:4)

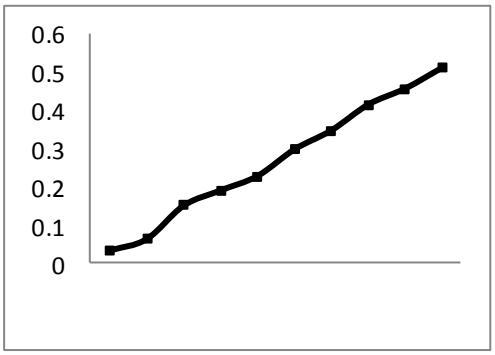


Fig: 4 - Dissolution curve of F1c (1:9)

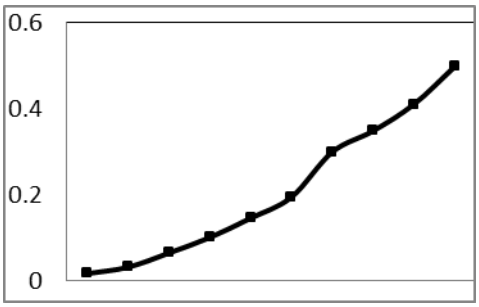


Fig : 5 - Dissolution curve of F2a (1:1)

Fig : 6 -Dissolution curve of F2b (1:4)

Fig :7 -Dissolution curve of F2c (1:9)

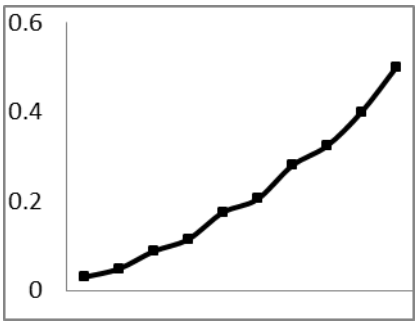


Fig: 8 -Dissolution curve of F3a (1:1)

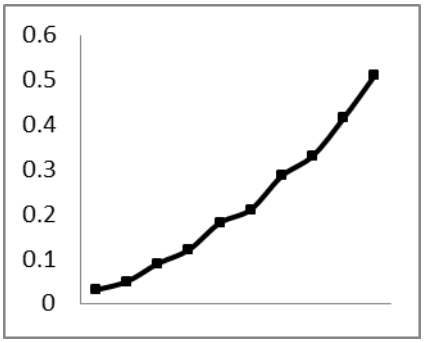


Fig: 9 - Dissolution curve of F3b (1:4)

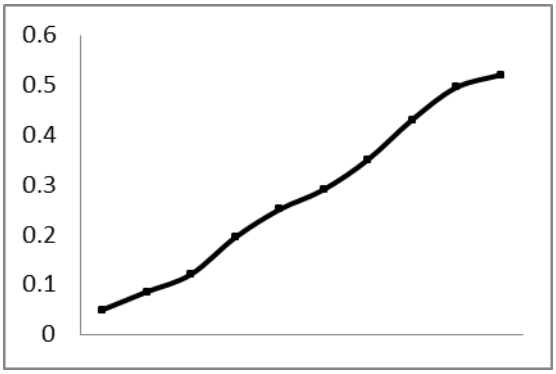


Fig: 10 -Dissolution curve of F3c (1:9)

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