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SOLID DISPERSION TECHNIQUE FOR SOLUBILITY ENHANCEMENT OF WEAKLY WATER SOLUBLE DRUG (NAPROXEN)

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ABSTRACT

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation for pharmacological response to be shown. pharmaceutical research that focus on improving the oral bioavailability of active agents include; enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly water soluble drugs. There are different techniques to enhance the solubility of drug, among these solid dispersions have been known to be one of the recent means of improving the dissolution rate by enhancement of solubility and hence the bioavailability of poorly water soluble drugs. 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 (clusters) or in crystalline particles.

KEYWORDS: Solubility, bioavailability, solid dispersions.

INTRODUCTION

Drug absorption sufficient and reproducible bioavailability, pharmacokinetic profile of orally administered drug substances is highly dependent on solubility of that compound in aqueous medium.[1] Poorly water-soluble drugs involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bio-availability.[2] 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 and enhancing permeability of poorly water soluble drugs.[3]

There are some different methods for enhancing the solubility of poorly water-soluble drugs among which solid dispersions have been known to be one of the recent means of improving the dissolution rate by enhancement of solubility and hence the bioavailability of poorly water soluble drugs. The term 'solid dispersion' has been utilized to describe a family of dosage forms whereby the drug is dispersed in a biologically inert matrix, usually with a view to enhancing oral bioavailability. Solid dispersions are "The dispersion of one or more active ingredients in an inert carrier or matrix, where the active ingredients could exist in finely crystalline, solubilised or amorphous state."

Application of solid dispersion[17]

1. To increase the solubility of poorly soluble drugs thereby increase the dissolution rate, absorption and bioavailability.
2. To stabilize unstable drugs against hydrolysis, oxidation, recrimination, isomerization, photo oxidation and other decomposition procedures.
3. To reduce side effect of certain drugs.
4. Masking of unpleasant taste and smell of drugs.
5. Improvement of drug release from ointment creams and gels.
6. To avoid undesirable incompatibilities.
7. To obtain a homogeneous distribution of a small amount of drug in solid state.
8. To dispense liquid (up to 10%) or gaseous compounds in a solid dosage.
9. To formulate a fast release primary dose in a sustained released dosage form.
10. To formulate sustained release regimen of soluble drugs by using poorly soluble or insoluble carriers.
11. To reduce presystemic inactivation of drugs like morphine and progesterone.
12. No change in chemical properties of the drug.

There are different methods for preparation of solid dispersions these are- fusion method, solvent evaporation method, melt solvent evaporation method, melt extrusion method, lyophilization method and melt agglomeration method. 22.

MATERIAL AND METHODS

Materials

Naproxen was procured as a gift sample from Dr. Reddy's lab, Hydrabad, polymers i.e. PEG 4000 from Samar Chemicals, Nagpur and poloxamer from Zim laboratory, Nagpur. All other materials were of analytical reagent grade.

Preparation of solid dispersion by solvent evaporation method

Solid dispersions of Naproxen were prepared by solvent evaporation method using PEG 4000 and Poloxamer, as carriers in combination at ratio (1:0.75:0.25, 1:0.5:0.5, 1:1:1) and individually at ratio (1:1, 1:1.5, 1:2). Naproxen and carriers were dissolved in common solvent i.e. methanol. The solvent was removed by evaporation on a water bath. The mixture was stirred during evaporation. The dried mass was stored over night in dessicator. The prepared SD was then grounded by using morter and pestle, sieved through mesh 40 and stored in dessicator for further use.

Preparation of Naproxen solid dispersion by Fusion method

Solid dispersions of Naproxen were prepared by fusion method using PEG 4000 and Poloxamer, as carriers in combination at ratio (1:1:0.5, 1:0.75:0.75, 1:0.5:0.5) and individually at ratio (1:1, 1:1.5, 1:2). Naproxen and carriers were accurately weighed according to weighed ratios. Carriers were melted according to their melting points and Naproxen was added to it. It was mixed well and flashed cooled in an ice bath and then stored over night in a dessicator. The prepared SD was pulverized, sieved through a mesh 40 and stored in a dessicator for further use.

RESULT AND DISCUSSION

Identification by FTIR spectroscopy

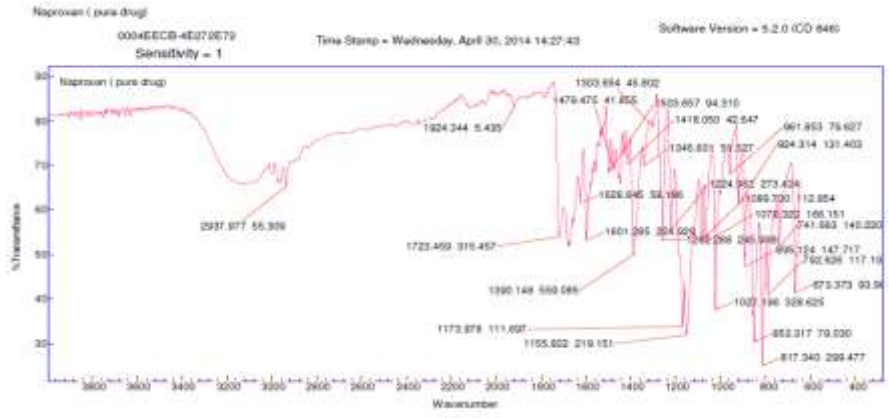

Figure 1. FTIR spectroscopy of Naproxen.

Table 1. Functional group detection of naproxen by FTIR.

Peak Name	Area	Height	Left Edge	Right Edge	Center
Peak1	-93.963	15.275	681.182	669.534	673.373
Peak2	-140.228	12.333	745.946	725.212	741.663
Peak3	-117.191	12.666	795.883	779.259	792.626
Peak4	-299.477	30.086	823.872	808.030	817.340
Peak5	-79.030	11.182	856.263	841.926	853.317
Peak6	-147.717	21.310	900.283	889.101	895.124
Peak7	-131.403	16.006	928.122	914.844	924.314
Peak8	-79.627	7.632	966.678	947.109	961.853
Peak9	-328.625	32.736	1033.188	1018.395	1027.196
Peak10	-166.151	14.735	1074.073	1054.737	1070.322
Peak11	-112.854	13.216	1094.924	1083.858	1089.730
Peak12	-219.151	14.386	1159.454	1140.118	1155.822
Peak13	-111.697	12.693	1180.421	1168.540	1173.976
Peak14	-273.424	21.501	1232.604	1215.598	1224.962
Peak15	-245.998	22.214	1267.782	1251.241	1262.288
Peak16	-45.802	3.896	1309.365	1295.038	1303.654
Peak17	-51.527	5.443	1348.969	1330.332	1345.601
Peak18	-558.085	25.663	1399.289	1371.217	1390.148
Peak19	-42.647	7.004	1422.236	1413.267	1416.050
Peak20	-41.855	5.400	1486.533	1475.701	1479.475
Peak21	-94.310	11.404	1508.665	1486.531	1503.657
Peak22	-224.929	17.968	1607.324	1580.901	1601.285
Peak23	-58.186	7.404	1631.438	1621.069	1628.645
Peak24	-315.457	19.431	1735.104	1713.322	1723.469
Peak26	-5.435	0.952	1930.248	1922.560	1924.344
Peak25	-55.309	4.827	2943.713	2926.474	2937.977

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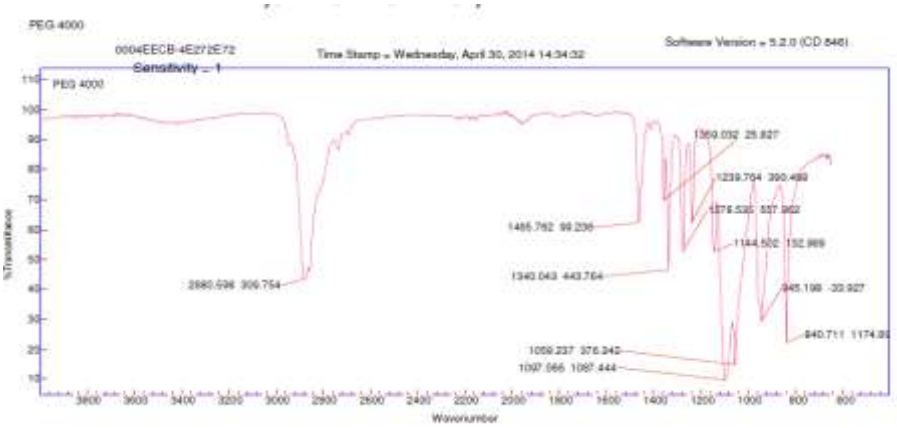

Figure 2. FTIR spectroscopy of PEG 4000.

Table 2. Functional group detection of PEG 4000 by FTIR.

Peak Name	Area	Height	Left Edge	Right Edge	Center
Peak1	-1174.893	54.379	853.807	798.246	840.711
Peak2	33.927	9.197	949.438	905.991	945.198
Peak3	-376.242	19.137	1062.775	1018.046	1058.237
Peak4	-1087.444	37.863	1114.492	1082.227	1097.066
Peak5	-132.969	20.782	1176.926	1138.371	1144.502
Peak6	-390.488	28.103	1248.096	1224.334	1239.764
Peak7	-557.862	37.217	1295.621	1267.549	1278.536
Peak8	-443.764	39.694	1346.057	1326.372	1340.043
Peak9	-25.827	15.770	1379.604	1355.608	1359.032
Peak10	-99.236	16.933	1483.621	1461.140	1465.762
Peak11	-309.754	12.577	2909.002	2872.776	2880.598

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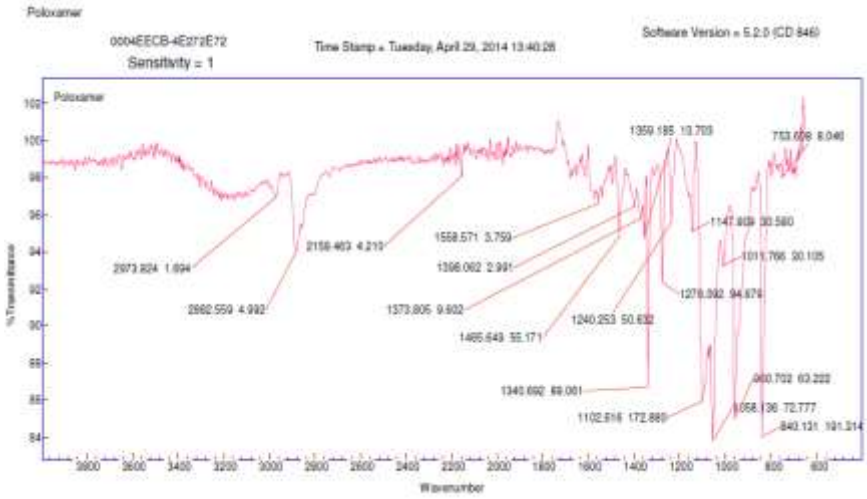

Figure 3. FTIR spectroscopy of poloxamer.

Table 3. Functional group detection of poloxamer by FTIR.

Peak Name	Area	Height	Left Edge	Right Edge	Center
Peak1	-8.046	1.076	757.126	747.926	753.608
Peak2	-191.314	14.522	846.818	826.318	840.131
Peak3	-63.222	7.094	970.755	955.146	960.702
Peak4	-30.105	1.921	1017.580	996.264	1011.766
Peak5	-72.777	6.364	1062.309	1045.535	1058.136
Peak6	-172.880	8.212	1116.822	1089.915	1102.616
Peak7	-30.580	2.957	1151.883	1139.419	1147.809
Peak8	-50.632	4.144	1246.466	1227.712	1240.253
Peak9	-84.679	6.753	1287.933	1266.617	1278.092
Peak10	-89.061	11.582	1345.708	1331.730	1340.692
Peak11	-13.703	2.522	1362.364	1354.910	1359.185
Peak12	-9.602	1.063	1382.050	1369.703	1373.805
Peak13	-2.991	0.536	1400.221	1394.164	1398.062
Peak14	-55.171	4.061	1475.118	1452.837	1465.649
Peak18	-3.759	0.800	1560.674	1553.187	1558.571
Peak17	-4.210	1.009	2160.177	2154.470	2158.463
Peak16	-4.992	0.476	2885.064	2873.416	2882.559
Peak15	-1.694	0.193	2983.550	2971.902	2973.824

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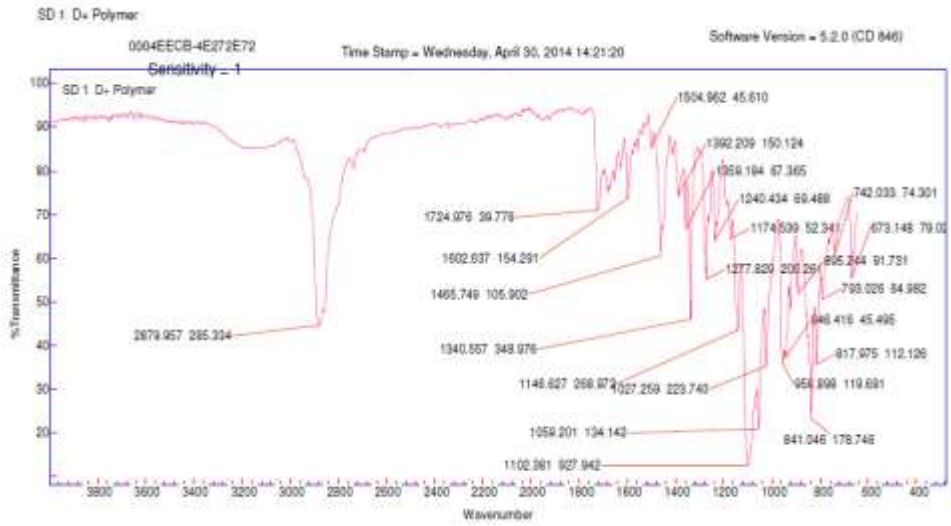

Figure 4. FTIR spectroscopy of SD1 (drug + polymer).

Table 4. Functional group detection of SD1.

Peak Name	Area	Height	Left Edge	Right Edge	Center
Peak1	-79.028	10.877	679.435	669.301	673.148
Peak2	-74.301	7.466	745.713	730.221	742.033
Peak3	-64.982	7.391	795.800	779.609	793.026
Peak4	-112.126	14.467	820.960	808.263	817.975
Peak5	-178.740	21.763	845.770	834.586	841.046
Peak6	-91.731	12.472	898.769	886.772	895.244
Peak7	-45.495	5.157	948.973	936.023	946.416
Peak8	-119.681	11.794	967.726	955.146	958.598
Peak9	-223.740	15.963	1031.208	1001.855	1027.259
Peak10	-134.142	13.470	1062.691	1047.283	1059.201
Peak11	-927.942	33.442	1116.765	1084.440	1102.381
Peak12	-268.972	20.126	1155.028	1138.720	1146.627
Peak13	-52.341	6.558	1180.188	1169.006	1174.539
Peak14	-69.488	10.252	1245.417	1235.633	1240.434
Peak15	-200.261	19.787	1287.234	1272.907	1277.829
Peak16	-348.976	33.886	1346.406	1326.372	1340.557
Peak17	-67.365	12.236	1363.529	1355.725	1359.184
Peak18	-160.124	10.250	1399.638	1380.070	1392.209
Peak19	-105.902	12.620	1479.777	1460.791	1465.749
Peak20	-45.610	5.819	1509.364	1499.230	1504.962
Peak21	-154.291	13.009	1608.256	1591.483	1602.637
Peak22	-39.776	5.284	1736.036	1722.641	1724.976
Peak23	-285.334	10.475	2905.974	2872.427	2879.967

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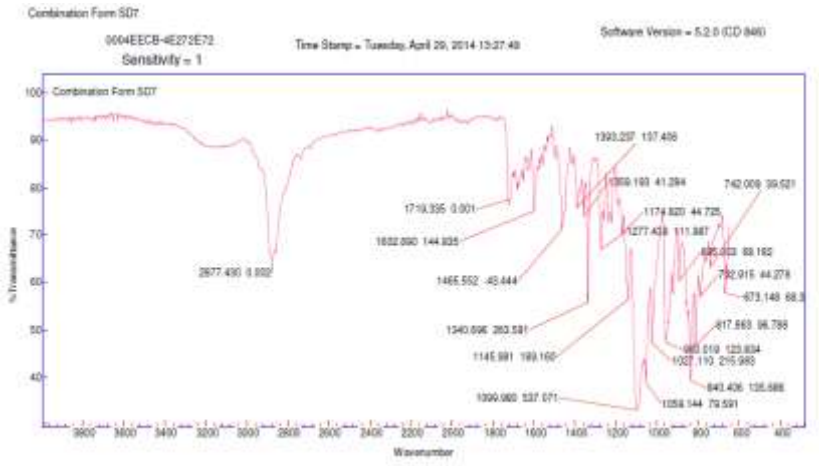

Figure 5. FTIR spectroscopy of SD7.

Table 5. Functional group detection of SD7.

Peak Name	Area	Height	Left Edge	Right Edge	Center
Peak1	-68.358	9.826	679.551	669.534	673.148
Peak2	-39.521	5.597	745.596	734.997	742.009
Peak3	-44.278	5.259	795.450	779.725	792.915
Peak4	-96.788	11.812	820.727	807.914	817.863
Peak5	-135.686	16.327	845.071	834.122	840.406
Peak6	-68.182	10.107	898.653	886.402	895.353
Peak7	-123.834	13.151	967.842	955.263	960.019
Peak8	-215.983	13.583	1031.208	1001.389	1027.110
Peak9	-79.591	8.056	1062.309	1047.166	1059.144
Peak10	-537.071	20.876	1115.774	1087.236	1099.980
Peak11	-189.160	14.064	1154.911	1138.720	1146.981
Peak12	-44.725	5.836	1180.188	1169.239	1174.620
Peak13	-111.987	11.915	1286.069	1273.023	1277.438
Peak14	-263.581	26.962	1346.523	1327.537	1340.696
Peak15	-41.284	7.716	1362.947	1355.725	1359.193
Peak16	-137.406	9.367	1400.104	1379.837	1393.237
Peak20	43.444	-0.009	1479.420	1465.559	1465.552
Peak17	-144.835	11.987	1608.373	1591.599	1602.690
Peak19	-0.001	0.006	1719.581	1719.299	1719.335
Peak18	-0.002	0.001	2878.307	2877.375	2877.430

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Resolution: 4 cm-1
System Status: Good
Method Name: ATR FTIR SNIOP
Apodization: Triangular
User: administrator

Table 6. Interpretation of FTIR peaks present in Naproxen.

Peaks (cm^{-1})	Characteristic functional group present in Naproxen
1262	Ether Aryl –o stretch
1723	Carboxyl group (-COOH) C=O stretch
2937	O –H Strech
743	Methylene –CH2-CH2- rocking
1155	C-N stretch of terniary amine nitrogen

From FTIR graph, it was seem that the peaks show there is no interaction between Naproxen and polymers (PEG 4000 and poloxamer) used in this study.

DERERMINATION OF SOLUBILITY

Table 7. Solubility of Naproxen.

Sr.No.	Particular	Solubility (mg/ml)	
		Distilled water	Phosphate buffer pH 7.4
1	Naproxen	4.6	43.75

Table 8. Solubility of Naproxen SDs prepared by SEM in phosphate buffer of pH 7.4.

Sr.No.	Type of SDs	Drug:Polymer ratio	Method	Solubility (mg/ml)	Increased
1	**SD1**	**1:1**	**SOLVENT EVAPORATION METHOD**	160	3.65Times
2	**SD2**	**1:1.5**		46	1.65
3	SD3	1:2		80	1.82
4	SD4	1:1		90	2.05
5	SD5	1:1.5		80	1.82
6	SD6	1:2		80	1.82
7	SD7	1:0.75:0.25		150	3.42
8	SD8	1:0.5:0.5		80	1.82
9	SD9	1:1:1		90	2.05

Table 9. Solubility of Naproxen SDs prepared by FM in phosphate buffer of pH 7.4.

Sr.No.	Type of SDs	Drug:Polymer ratio	Method	Solubility (mg/ml)	Increased
1	SD10	1:1	FUSION METHOD	58	1.32 Times
2	SD11	1:1.5		140	3.2
3	SD12	1:2		60	1.37
4	SD13	1:1		80	1.82
5	SD14	1:1.5		52	1.18
6	SD15	1:2		120	2.74
7	SD16	1:1:0.5		70	1.6
8	SD17	1:0.75:0.75		80	1.82
9	SD18	1:0.5:0.5		80	1.82

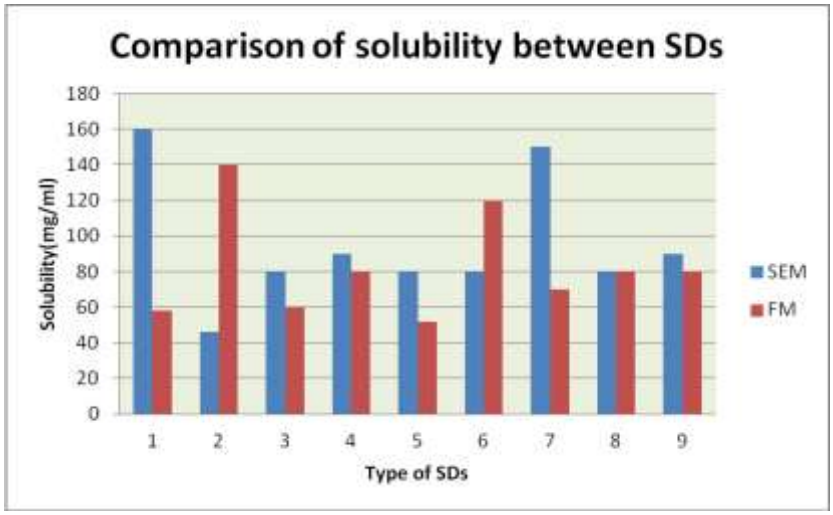

Figure 6. Comparative study of Naproxen SDs solubility in phosphate buffer of pH 7.4.

Table 10. Precompression parameter of powder blend.

Batch code	Bulk density (gm/cm^3)	Tapped density(gm/cm^3)	Carr's Index (%)	Hausner's ratio	Angle of Repose (Θ)
F1	0.43	0.57	24.56	1.32	36.86^0
F2	0.47	0.54	12.96	1.15	34.25^0

F1 contains solid dispersion SD1 and **F2** contains solid dispersion SD7.

Table 11. Evaluation results of tablet from batch F1 and F2.

Parameter	F1	F2
Thickness (mm)	6.4	6.5
Diameter (mm)	10	10
Hardness (kg/cm^2)	6.2	6
Friability (%)	0.64	0.48
Average weight (mg)	600	590
Disintegration time (min)	10	12

Table 12. Cumulative drug release data of tablet batches.

Time (Minute)	Cumulative drug release data		
0	F1	F2	Naprosyn (Marketed)
5	7.447	5.058	28.267
10	29.641	22.812	72.669
15	45.033	43.974	82.306
30	74.777	87.734	87.859
45	94.656	102.166	92.052
60	97.832	102.962	92.495

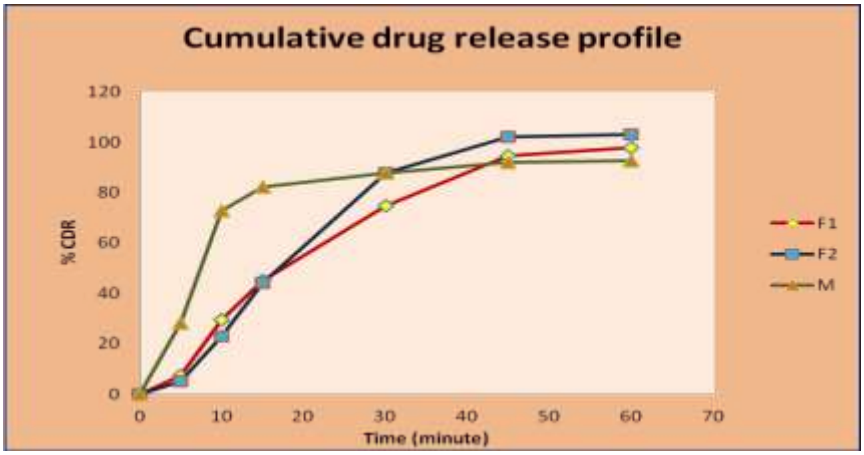

Figure 7. % Cumulative drug release data of tablet batches.

From above dissolution study it was found that F2 tablet had shown maximum drug release 102.96% within 60 minutes, where as F1 and Marketed (M) tablets had shown maximum release 97.83% and 92.45% in 60 minute respectively.

SUMMARY AND CONCLUSION

The present investigation deals with the formulation and evaluation of solid dispersion of Naproxen by Solid Dispersion Techniques using two polymers PEG 4000, Poloxamer and combination of PEG 4000 and Poloxamer. Solid dispersions were prepared by two methods such as solvent evaporation method and fusion method. The study reveals that the drug release from formulations is dependent on formation of amorphous solid dispersion, reduced particle size, improved wet ability, particle with higher porosity and formation of hydrophilic amorphous product.

SD1 containing PEG 4000 with drug: polymer in 1:1 proportion and SD7 containing PEG 4000: Poloxamer with drug: polymer in 1:0.75:0.25 i.e. Drug : Polymer in 1:1 ratio prepared by solvent evaporation method are the best formulation among all SDs. Finally, SDs with shigher solubility among different ratios of drug and polymers alone and in combinations were selected for tablet manufacturing. Tablets of optimized formulations of SDs were prepared by using MCC, Cross povidone, talc and magnesium stearate as excipients and performed various evaluations, which were found to be in limit prescribed in official books. The optimized formulations F1 and F2 were compared with marketed tablet Naprosyn.

Promising results had been obtained in dissolution enhancement of Naproxen with use of poloxamer and PEG 4000. Such polymers or carriers mentioned in this study if further studied carefully can be used as platform, which can be effectively used for dissolution

enhancement of any BCS Class II drugs. A higher solubility and dissolution rate were obtained with solid dispersions prepared using combinations of polymers in a ratio of 1:0.75:0.25 for the drug, PEG 4000 and poloxamer respectively showing more drug release rate i.e 102.96% within 60 minutes.

Based on the study it may be concluded that Naproxen tablets can be prepared by solid dispersion was found to be ideal for improving the dissolution rate.

FUTURE SCOPE

A number of synthesized chemical molecules suffer from low aqueous solubility problems. Although these molecules have potential pharmacodynamic property, they show low bioavailability due to poor aqueous solubility, and these molecules become unsuccessful to reach the market. Thus enhancement of aqueous solubility, dissolution rate and bioavailability of drug is a very challenging task in drug development.

Considering the need of pharmaceutical industry, a dissolution enhancement is potential area and has higher scope of patentability. Especially the dissolution enhancement by simpler method is more beneficial for the industrial scale up. In coming year's dissolution enhancement of drug by using polymers, surfactants and different carriers will be appreciated.

And in future the in vitro dissolution studies need to be correlated with in vivo bioavailability studies to prove the advantages of the developed formulation.

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