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Study on the effect of different polymers on *in-vitro* dissolution profile of Fenofibrate by solid dispersion technique

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ABSTRACT

Fenofibrate is a poor water soluble drug having poor rate of dissolution. In this research work we tried to enhance dissolution of fenofibrate by following solid dispersion of fenofibrate formulations with different dissolution enhancing polymers likeHPMC 6cps, Poloxamer 188, Poloxamer 407, PEG 6000. Total twenty four formulations were prepared with this polymers in single or combinations. If the solid dispersion is first, other parameters like dissolution, bioavailability will be first. Dissolution of all the formulations were tested for % drug release profile, mean dissolution time, assay and uniformity of drug content and % recovery was calculated. From all formulations, F3, F5, F6, F9, F10, F12 and F14 shows greater dissolution of fenofibrate 93.64%, 83.66%, 100.53%, 100.61%, 100.95% and 83.06% respectively within 60 minutes of dissolution and also decreases the mean dissolution time. Based on in-vitro dissolution results and drug release model kinetics, we can decide that these formulations are able to increase the dissolution as well as can increase the absorption rate and bioavailability of fenofibrate. Finally we can conclude that, these formulations enhance the dissolution and bioavailability of Fenofibrate and good formulation candidates for Fenofibrate in future.

INTRODUCTION

Solid dispersion is drug dispersed in a biologically inert polymer matrix (Chiou and Riegelman, 1971), a solid dispersion is "the dispersion of one or more active ingredients in an inert carrier at solid-state prepared by melting (fusion), solvent or the melting-solvent method". The term 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. The carrier used has traditionally been a water-soluble or water-miscible polymer such as polyethylene glycol (PEG) or polyvinylpyrrolidone (PVP) or low molecular weight materials such as urea, citric acid and mannitol. However, recent technology advancement shows that, water-insoluble matrices such as Gelucires can also be included to produce solid dispersions (Craig, 2002). Based on their molecular arrangement, six different types of solid dispersions methods used for preparation of solid dispersion system.

These methods are simple eutectic mixture (Craig, 2002), amorphous precipitation in a crystalline carrier (Martin et al., 1993), solid solution (Chiou and Riegelman, 1971), glass solution (Taylor and Zografi, 1997), glass suspension (Craig, 2002), compound or complex formation (Bochner et al., 1977) respectively. Formulation of drugs as solid dispersions offers a variety of processing and excipient options that allow for flexibility when formulating oral delivery systems for poorly water soluble drugs. This strategy includes complete removal of drug crystallinity, and molecular dispersion of the poorly soluble compound in a hydrophilic polymeric carrier. When the solid dispersion is exposed to aqueous media, the carrier dissolves and the drug releases as fine colloidal particles. The resulting enhanced surface area produces higher dissolution rate and bioavailability of poorly water-soluble drugs.

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Drug in soluble hydrophilic carrier improves the dissolution rate by reducing particle size, higher porosity, drug is in amorphous state, improving wet-ability and hence possibly bioavailability for poorly water soluble drugs.The potential of this technique to increase oral absorption and hence bioavailability is enormous. Fenofibrate stimulates the activity of peroxisome proliferator-activated receptor-α (PPAR-α), a member of the PPAR subfamily of nuclear receptors that modulate the transcription of genes that regulate fatty acid and cholesterol metabolism (Staels et al., 1998). Fenofibrate a pro-drug, pharmacologically inactive and it also undergoes rapid hydrolysis at the ester bond to form the active metabolite fenofibric acid (Adkins and Faulds, 1997). Fenofibrate is a neutral, lipophilic compound that is practically insoluble in water, it challenging us to constantly achieve bioavailability and therapeutic levels (Vogt, 2008).

MATERIALS AND METHOD

Materials

Active drug Fenofibrate from ACI Pharmaceuticals Limited. Polymers HPMC 6cps, Poloxamer 188, Poloxamer 407, PEG 6000 from BASF. Solvents like methanol and absolute ethanol from merck, Germany. Sodium Lauryl Sulphate and HCl from LobaChemie, India.

Formulation

Formulations were design with different solubility enhancing polymers in single or combinations with drug. In single formulations drug polymer ratio was 1:2, 1:3 and 1:4, with all polymers. Combined 12 formulations were designed. Formulations are Fenofibrate: PEG 6000: Poloxamer 407 = 1:3:0.5 & 1:3:1, Fenofibrate: PEG 6000: Poloxamer 188 = 1:3:0.5 & 1:3:1, Fenofibrate: Poloxamer 407: PEG 6000 = 1:3:0.5 & 1:3:1, Fenofibrate: Poloxamer 407: Poloxamer 188 = 1:3:0.5 & 1:3:1, Fenofibrate: Poloxamer 188: PEG 6000 = 1:3:0.5 & 1:3:1, Fenofibrate: Poloxamer 188: Poloxamer 407 = 1:3:0.5 & 1:3:1. Formulations are summarized as table 1 and table 2.

Preparation of Solid Dispersion by Solvent Method

(Lachmanand Lieberman, 1970**)**

The solvent process either comprises dissolving a sparingly water-soluble drug and a water-soluble polymer, i.e. the carrier, in an organic solvent capable of dissolving both and removing the solvent by evaporation or dissolving the drug in an organic solvent, dispersing the solution in the carrier and removing the solvent by evaporation to provide the desired solid dispersion. The following general procedure was followed 400mg of fenofibrate was taken in the beaker. 8ml ethanol was added in each. Drug was completely dissolved in the solvent. Different types of polymer were added in the solution at specific amount according to formulation. Then sonicate it for 5 minutes. All solutions were kept at normal environment for 2 hours, after that kept intooven at 60°C temperature for 2 days. When the solutions were evaporated completely, they were stored in desiccators. The formulations were withdrawn from vials and crushed in mortar and pestle and then passed through 150 micron sieve. Then formulations were transferred in vials and stored in desiccators. This same basic procedure was followed for all formulations.

In-Vitro Study of Fenofibrate Dissolution from Solid Dispersion (Lachmanand Lieberman,1970; Shargel and Susanna, 2005)

Dissolution Medium 0.05 M Sodium Lauryl Sulphate, Apparatus USP-II, Paddle type.Stirring Speed 50 rpm for 1 Hour.

Preparation of 0.05 M Sodium Lauryl Sulphate

14.419gm of Sodium Lauryl Sulphate was dissolved in 1000 ml of distilled water to produce 0.05 M Sodium Lauryl Sulphate.

Preparation of sample of each formulation:

Each sample is placed in 900 ml of dissolution medium, at 37 ± 0.5°C. Sample is withdrawn by a syringe at 5, 10, 20, 30, 45, 60 minutes and replaced with equal amount of dissolution medium. Sample is filtered with 0.45µ filter paper. 2 ml of the filtered sample is taken in a 25 ml of volumetric flask and full volume with dissolution medium. Absorbance values of the solution were determined with the help of UV-spectrophotometer (UV-mini-1240, SHIMADZU CORP., Kyoto, Japan) at λmax 286nm, using 0.05 M Sodium Lauryl Sulphate solution as blank against the calibration curve.

Assay (USP, 2001; Shargel and Susanna, 2005)**:**

Assay of each formulations were performed to determine amount of drug present in the formulation and to determine drug content uniformity.

RESULT AND DISCUSSION

To overcome the problems with solubility of fenofibrate solubility was the prime aim of our research work. Different types of methods are established to enhance solubility of poor soluble drug, solid dispersion is one of them and we tried to enhance dissolution of drug by following this method. Different formulations (total 24) were designed with different dissolution enhancing polymers (table 1 & 2). All formulations are uniform in drug content. Dissolution profile, mean dissolution time, assay was performed and % recovery of drug was calculated. Among all formulations (F1 to F12), we have used 66.7%, 75% and 80% of different polymers shows the enhanced dissolution of fenofibrate. Drug polymer ratio was 1:2, 1:3 and 1:3. Mean dissolution time (MDT) decreases with the increasing polymer load in all formulations except Poloxamer 188. That means if the polymer load was increased, solubility of the active ingredient increased in a step wise fashion. They also lowers MDT values, were obtained in case of 80% of all polymers. So, it can be said that drug release increasing capacity of HPMC6cps, PEG6000, Poloxamer188 and Poloxamer407 increases with increasing quantity (table 3, figure 1 and table 5).

Table. 1A: Formulation F1-F12.

	Formulation											
Ingredients (mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Fenofibrate	200	200	200	200	200	200	200	200	200	200	200	200
HPMC 6cps	400				600				1200			
PEG 6000		400				600				1200		
Poloxamer 407			400				600				1200	
Poloxamer 188				400				600				1200
Ethanol (ml)	8	8	8	8	8	8	8	8	10	10	10	10

Table. 1B: formulation F13-F24.

Formulation	**Fenofibrate : PEG 6000 : Poloxamer 407**		**Fenofibrate : PEG 6000 : Poloxamer 188**		**Fenofibrate : Poloxamer 407 : PEG 6000**		**Fenofibrate : Poloxamer 407 : Poloxamer 188**		**Fenofibrate : Poloxamer 188 : PEG 6000**		**Fenofibrate : Poloxamer 188 : Poloxamer 407**	
Ratio	1:3:0.5	1:3:1	1:3:0.5	1:3:1	1:3:0.5	1:3:1	1:3:0.5	1:3:1	1:3:0.5	1:3:1	1:3:0.5	1:3:1
Ingredient (mg)	F13	F14	F15	F16	F17	F18	F19	F20	F21	F22	F23	F24
Fenofibrate	200	200	200	200	200	200	200	200	200	200	200	200
Poloxamer 188			100	200			100	200	600	600	600	600
Poloxamer 407	100	200			600	600	600	600			100	200
PEG 6000	600	600	600	600	100	200			100	200		
Ethanol (ml)	8	8	8	8	8	8	8	8	8	8	8	8

Table. 3: Dissolution profile of formulations F1-F12.

Time	**% Drug Released**												
	Without polymer	**F1 (66.67%)**	**F2 (75%)**	**F3 (80%)**	**F4 (66.67%)**	**F5 (75%)**	**F6 (80%)**	**F7 (66.67%)**	**F8 (75%)**	**F9 (80%)**	**F10 (66.67%)**	**F11 (75%)**	**F12 (80%)**
		y = 0.769x + 17.01	**y = 1.019x+ 17.25**	**y = 1.445x + 17.79**	**y = 0.795x + 18.89**	**y = 1.035x + 33.67**	**y = 0.964x + 58.32**	**y = 0.784x + 22.36**	**y = 0.766x + 33.97**	**y = 0.964x + 58.32**	**y = 0.757x + 26.85**	**y = 0.887x + 32.95**	**y = 0.983x + 37.18**
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	13.6	22.78	23.2	28.06	23.73	45.51	81.95	31.44	48.12	93.03	36.84	45.67	51.35
10	26.2	32.43	34.14	38.95	35.47	58.27	96.81	39.83	55.97	99.86	46.64	55.18	63.68
20	40.32	40.49	47.67	53.22	44.85	69.77	96.87	47.42	62.58	100.51	53.68	64.79	71.24
30	48.33	47.06	55.86	68.99	50.76	76.78	97.02	53.28	65.33	100.57	56.29	69.49	77.53
45	51.73	51.57	63.85	87.5	55.47	78.78	99.08	56.22	66.54	100.6	60.39	72.49	80.56
60	54.37	54.67	69.32	93.64	57.13	83.66	100.53	61.61	69.5	100.61	62.95	73.94	83.06

Tabel. 4: Dissolution profile of formulations F13- F24.

Time	**% Drug Released**												
	Without polymer	**F13 (11.11%)**	**F14 (20%)**	**F15 (11.11%)**	**F16 (20%)**	**F17 (11.11%)**	**F18 (20%)**	**F19 (11.11%)**	**F20 (20%)**	**F21 (11.11%)**	**F22 (20%)**	**F23 (11.11%)**	**F24 (20%)**
0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	13.6	48.42	62.75	33.13	34.1	27	50.96	39.63	45.05	29.98	25.76	21.37	39.99
10	26.2	53.46	80.07	45.21	43.602	29.55	66.99	56.53	59	64.81	35.44	33.03	50.22
20	40.32	56.93	83.01	47.52	47.635	34.93	70.88	62.12	61.5	36.04	.5.72	42.34	53.31
30	48.33	59.61	86.8	50.72	50.17	44.88	73.51	63.15	65.1	37.44	36.39	48.43	55.8
45	51.73	60.62	86.92	54.31	51.06	52.68	73.74	63.17	67.88	37.57	37.45	51.54	56.12
60	54.37	63.61	88.72	54.58	61.08	57.75	79.01	63.28	68.84	37.41	39.15	53.84	57.9

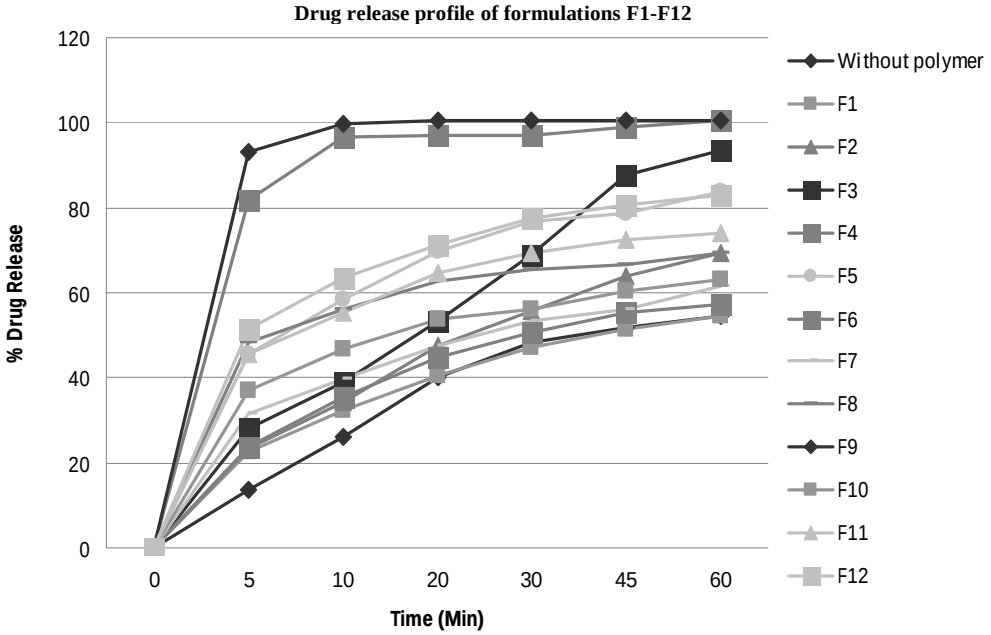

Fig. 1: Drug release profile of single polymer containing formulations.

Table. 5: MDT (Mean Dissolution time) of all formulations.

Formulation			$T_{25\%}$ (Min)	$T_{50\%}$ (Min)	$T_{80\%}$ (Min)
HPMC6cps		F-1	5.54	74.15	151.08
		F-5	5.23	37.12	73.14
		F-9	4.07	11.66	21.58
PEG6000		F-2	4.63	68.61	114.24
		F-6	0.325	21.77	43.13
		F-10	$3.38x10^{-8}$	2.77	5.82
Poloxamer188		F-3	1.86	21.42	42.04
		F-7	0.083	180.54	301.65
		F-11	6.27	61.73	113.54
Poloxamer407		F-4	0.6	84.15	166.97
		F-8	0.19	36.86	72.04
		F-12	0.08	21.29	41.13
PEG6000	Poloxamer407	F-13(11.11%)	0.007657	443.7529	551.1247
		F-14(20%)	0.001508	12.96272	19.28788
PEG6000	Poloxamer188	F-15(11.11%)	0.706545	191.1832	367.2822
		F-16(20%)	0.839343	152.3543	298.6771
Poloxamer407	PEG6000	F-17(11.11%)	5.041975	89.99246	184.7279
		F-18(20%)	0.012902	44.22912	71.2063
Poloxamer407	Poloxamer188	F-19(11.11%)	0.154523	81.57395	150.6771
		F-20(20%)	0.071151	69.45527	123.1177
Poloxamer188	PEG6000	F-21(11.11%)	0.324482	369676.1	334873.5
		F-22(20%)	1.947244	5443.908	8911.02
Poloxamer188	Poloxamer407	F-23(11.11%)	5.76533	69.36209	140.7988
		F-24(20%)	0.09331	319.8656	514.965

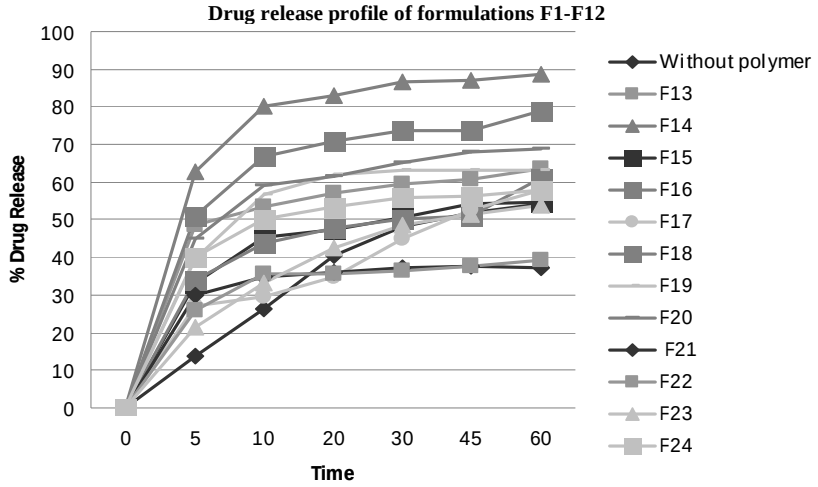

Fig. 2: Drug release profile of combined formulations.

Table. 6: Assay and % Recovery of all formulations.

Formulation	Labeled Amount (mg)	Amount Found (mg)	% Recovery
F1	200	205	102.5
F2	200	198	99
F3	200	195	97.5
F4	200	196	98
F5	200	198	99
F6	200	197.5	98.75
F7	200	198.6	99.3
F8	200	197.2	98.6
F9	200	210	105
F10	200	195.6	97.8
F11	200	198.7	99.3
F12	200	195.4	97.7
F13	200	186	93
F14	200	188	94
F15	200	182.2	91.1
F16	200	187	93.5
F17	200	195.5	97.75
F18	200	198.6	99.3
F19	200	194.5	97.2
F20	200	193.5	96.7
F21	200	191.5	95.7
F22	200	196.5	98
F23	200	192.1	96

Polymer combinational formulations (F13-F24) show poor dissolution than single polymer containing formulations. Only F13 and F14 mean dissolution time for fenofibrate decreases significantly for PEG6000 and Poloxamer 407 combination. From all the experimental data it can be stated that Poloxamer 188 is not useful in increasing solubility of fenofibrate, when used in combination with other polymers.PEG 6000 and Poloxamer 407 combination can be used. Optimum dissolution profile can be obtained with combination with higher percentage of PEG 6000 (Table 4, Fig. 2 and Table 5)

From data we summarize that form the 24 formulations only F3, F5, F6, F9, F10, F12 and F14 shows greater dissolution of fenofibrate 93.64%, 83.66%, 100.53%, 100.61%, 100.95% and 83.06% respectively within 60 minutes of dissolution.

CONCLUSION

Rapid dissolution, less mean dissolution time of formulations is able to produce the rapid bio-availability. Formulations with less mean dissolution time and enhanced dissolution may be suitable candidate for the formulation and preparation of fenofibrate in near future.

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