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SOLID DISPERSION BASED TABLETS OF POORLY SOLUBLE DRUG FLURBIPROFEN

Hemangi J Patel [1], Piyush Tiwari[1], Jitendra S Patel[1]

1. Bhabha Pharmacy Research Institute, Bhopal, MP

ABSTRACT

Flurbiprofen Non-steroidal anti-inflammatory drugs (NSAIDS) drug has half-life of about 3 to 6 hrs. The present study aims to formulate and evaluate poorly soluble drug Flurbiprofen using solid dispersion based tablet. Various studies have been done in attempt to improve the solubility's of Poorly water soluble drugs. The advent of solid dispersion technique provides a unique approach to particle size reduction and increased rates of dissolution. The compatibility studies of the drug and polymers were studied by IR spectroscopy and results suggested no interaction between drug and polymers. Solid dispersions of Flurbiprofen were prepared by common solvent method using Hydroxy Propyl Cellulose (HPC), Polyvinyl Pyrrolidone K-30(PVP) and Mannitol Fast dissolution observed with Mannitol as compared to HPC and PVP. Formulations F3, F6 and F9 containing PVP, HPC and Mannitol along with drug in 1: 6 ratios were used to formulate tablets. Formulation F9 containing drug and Mannitol showed highest dissolution of 81.11% in 1 hour due to amorphous nature of drug in presence of polymer. Formulation F3 containing drug and PVP in 1 : 6 ratio showed 73.05% drug release because of the formation of aggregates. Formulation F6 containing drug and HPC showed only 61.65% drug release due to the crystalline of the drug, low solubility of the drug. Results indicate that formulations prepared by the technique of solid dispersion showed increase in the dissolution of Poorly water soluble drug.

Key word: Solid dispersion; Flurbiprofen; Micronization; Compatibility studies.

*Corresponding Author Email: piyush.tiwarig@gmail.com
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INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDS) are a group of unrelated organic acids that have analgesic, anti-inflammatory and antipyretic properties. NSAIDs are the inhibitors of enzyme cyclo-oxygenase, which results in the direct inhibition of the biosynthesis of prostaglandins and thromboxanes from arachidonic acid[1].

The term solid dispersion may be defined as the dispersion of one or more active ingredients in an inert carrier or matrix at solid state prepared by the fusion or melting solvent method[2].

It is important that the carrier chosen for the solid dispersion system should be readily soluble in water. Additionally it should be stable at the processing temperature, easily form one or the other types of dispersion and has to be chemically and pharmacologically inert[3].

Flurbiprofen is a white or almost white, crystalline powder practically insoluble in water, freely soluble in alcohol and in methylene chloride. It dissolves in aqueous solutions of alkali hydroxides and carbonates. It is used in musculoskeletal and joint disorders such as ankylosing spondylitis, osteoarthritis and migraine. It is given in usual doses of 150 to 200 mg daily by mouth in divided doses. The solid dispersions of the Flurbiprofen prepared by using various polymers were further used for preparing tablets of Flurbiprofen. [4,5,6,7]

The present study aims to formulate and evaluate poorly soluble drug Flurbiprofen using solid dispersion based tablet.

MATERIALS AND METHODS

Flurbiprofen I.P. was a gift sample from Alembic Pharmaceuticals Ltd., Baroda. Other ingredient used in present work were either of LR/AR grade.

Preparation of Solid Dispersions:

Common solvent method:

For each formulation the drug (Flurbiprofen) and the carriers were selected in a ratio as mentioned in the Table 1.They were mixed in a beaker containing alcohol to form a clear solution. The solvent was removed by evaporation at 40^0C, while mixing.The mass obtained was crushed, pulverized and sieved through sieve no.100.

Physical Mixture Method:

The drug and the carriers in various proportions as mentioned in Table.1 were mixed to form uniform physical mixture dispersions.

Table 1: Formulation of Solid Dispersions of Flurbiprofen using Various Polymers

Formulation Code	Drug-Carrier	Ratio of Drug : Carrier
F1	Flurbiprofen-PVP	1 : 2
F2	Flurbiprofen-PVP	1 : 4
F3	Flurbiprofen-PVP	1 : 6
F4	Flurbiprofen-HPC	1 : 2
F5	Flurbiprofen-HPC	1 : 4
F6	Flurbiprofen-HPC	1 : 6
F7	Flurbiprofen-Mannitol	1 : 2
F8	Flurbiprofen-Mannitol	1 : 4
F9	Flurbiprofen-Mannitol	1 : 6

Preparation of Tablets from the Solid dispersions:

The solid dispersions of the Flurbiprofen prepared by using various polymers were further used for preparing tablets of Flurbiprofen. Formulations F3, F6 and F9 containing highest concentration of polymers were chosen for preparation of tablets.

Method of Preparation of Tablets:

Accurately weighed quantity of solid dispersion equivalent to 100 mg of Flurbiprofen was taken. Specified quantities of microcrystalline cellulose and lactose were added and mixed thoroughly and then ground to fine particle size. The starch paste was added in small proportions until wet dough like mass/ was formed. The wet mass was passed through Sieve No.16. The sieved granules which were wet were dried in a hot air oven at 60^0C for about 30 minutes. Intermittently the granules were mixed to ensure uniform drying. The dried granules were lubricated with Talc and Magnesium stearate and blending was done for 10 minutes. The lubricated granule blend was compressed into tablets on a RIMEK-10 station Rotary Compression machine.The formula for preparing Flurbiprofen 100 mg tablets was mentioned in the Table 2. The total weight of the tablet was adjusted to 800mg.

Table 2: The formula for preparing Flurbiprofen 100 mg tablets

Ingredients	Qty .taken
1) Flurbiprofen	S.D. ≅ 100 mg of Flurbiprofen
2) Microcrystalline cellulose	5%
3) Lactose	q.s
4) Starch paste	5%
5) Talc	0.75%
6) Magnesium stearate	0.25%

RESULTS AND DISSCUSION

Flurbiprofen a propionic acid derivative is a poorly water soluble drug. Various techniques have been mentioned in literature to improve the solubility and dissolution of poorly water soluble drugs. One such technique is solid dispersion.

In the present work; The identity of Flurbiprofen was confirmed in PVP, Mannitol and HPC dispersions by I.R. It was observed from I.R. spectral studies that these carriers were suitable for preparing solid dispersion. The water-soluble carriers like PVP, HPC and Mannitol which were selected for solid dispersion of the drug did not show any interaction which is evident from the I.R. spectral studies.

The solubility data revealed that the solubility of the drug increased in presence of these carriers. The solubility of the drug markedly increased in presence of all these polymers and was found to be more in pH 7.2 phosphate buffers as compared to 0.1N HCl and distilled water. The result was shown in Table 3 and graphical was shown in Figure 1.

Table 3: Solubility Data of Flurbiprofen and its Solid Dispersions

System	Solubility in gm/100 ml		
	0.1N HCL	Distilled water	pH 7.2 phosphate buffer
Drug	0.010	0.024	0.036
Drug – PVP	0.052	0.099	0.185
Drug – HPC	0.022	0.081	0.125
Drug – Mannitol	0.084	0.121	0.240

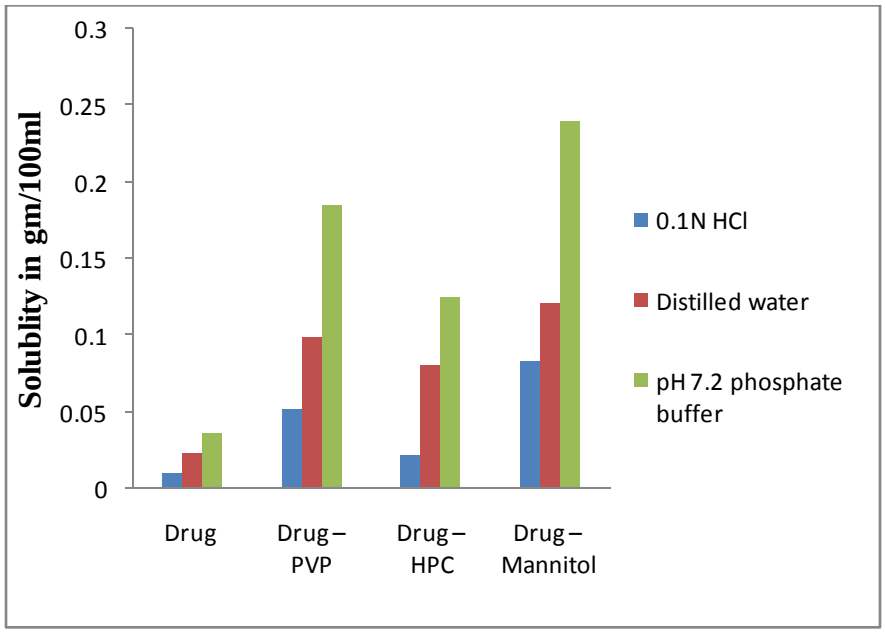

Figure 1: Solubility Profile of Flurbiprofen and Its Solid Dispersion Systems.

The Flurbiprofen content in solid dispersion systems was analyzed for its uniform distribution. The low percentage of deviation in the content uniformity indicated that the drug was uniformly distributed in all the formulations.

The dissolution studies of Flurbiprofen S.D. systems was carried out. The dissolution of the drug from the physical mixtures was determined by using Type-1 (basket) and Type-2 (paddle) apparatus. The in-vitro dissolution studies of solid dispersions prepared confirmed the fact that one can successfully enhance the dissolution of a poorly water-soluble drug like Flurbiprofen, thereby increasing its therapeutic efficacy among the three carriers used Mannitol gave the highest dissolution followed by PVP and HPC.

Flurbiprofen: Mannitol solid dispersions in 1:6 ratio showed highest dissolution followed by Flurbiprofen – Mannitol 1:4, Flurbiprofen – Mannitol 1:2, Flurbiprofen – PVP solid dispersions, Flurbiprofen – HPC dispersions. There was a 5-fold increase in the dissolution of the drug from the solid dispersion systems as compared to pure drug. The physical mixtures of the drug and the polymers also showed an increase in dissolution rate, but the dissolution was low as compared to solid dispersion system. The solid dispersion systems of these polymers in 1: 6 ratios were selected for preparation of tablets. In-vitro Dissolution Parameters of all Formulations Prepared (S.D. Systems and Physical Mixtures) shown in Table 4.

The release of the drug from the solid dispersion systems followed first order kinetics. Formulations F3, F6 and F9 containing PVP, HPC and Mannitol along with drug in 1: 6 ratios were used to formulate tablets. The evaluation parameter like Thickness (mm), Diameter (mm), Weight variation, Hardness (kg/cm^2), Disintegration Time (min), Friability (%), Content Uniformity, Cum. % Drug Released for selected formulation was shown in Table 5.

Table 4 In-vitro Dissolution Parameters of all Formulations

Formulation	Method	Cum. % Drug Released	Cum. % Drug Retained	Dissolution Rate ($g^{1/3}$ /min)	Dissolution Efficiency DE^{60} %	T^{50} (min)	T^{90} (min)
F1	Common Solvent	41.08	58.92	0.79×10^{-3}	31.66	44	101
F2		77.58	22.42	1.56×10^{-3}	56.66	47	101
F3		89.12	10.88	2.15×10^{-3}	75.00	40	97
F4		38.78	61.22	0.65×10^{-3}	28.33	47	98
F5		66.17	33.83	1.28×10^{-3}	48.33	47	103
F6		86.78	13.22	1.93×10^{-3}	68.33	40	103
F7		47.9	52.10	0.83×10^{-3}	36.66	48	105
F8		82.21	17.79	1.85×10^{-3}	66.66	41	106
F9		96.01	3.93	2.61×10^{-3}	86.66	37	96

F1		38.71	61.29	0.61×10^{-3}	23.33	54	104
F2		61.59	38.41	1.16×10^{-3}	43.33	47	102
F3		82.16	17.84	1.70×10^{-3}	61.66	45	101
F4	Physical	34.13	65.87	0.50×10^{-3}	20.00	62	107
F5	Mixture	59.29	40.71	1.05×10^{-3}	41.66	50	105
F6	Basket	79.85	20.15	1.63×10^{-3}	56.66	47	103
F7		43.32	56.68	0.70×10^{-3}	30.00	47	104
F8		68.48	31.52	1.42×10^{-3}	51.66	45	100
F9		86.73	13.27	1.91×10^{-3}	65.00	45	102
F1		38.73	61.27	0.58×10^{-3}	25.00	54	90
F2		56.99	43.01	1.07×10^{-3}	38.33	61	100
F3		82.12	17.88	1.51×10^{-3}	56.66	42	102
F4	Physical	34.78	65.22	0.59×10^{-3}	23.33	53	106
F5	Mixture	60.64	39.36	1.10×10^{-3}	38.33	51	103
F6	Paddle	77.59	22.41	1.58×10^{-3}	56.66	41	101
F7		45.61	54.39	0.82×10^{-3}	31.66	48	106
F8		72.98	27.02	1.41×10^{-3}	51.66	49	104
F9		88.99	11.01	1.86×10^{-3}	65.00	47	98
Pure Drug		27.37	72.63	0.37×10^{-3}	18.33	40	90

Table 5. Evaluation Parameters of Tablets.

Parameter	**Formulations**		
	F3	***F6***	***F9***
1) Thickness (mm)	6.15	6.12	6.12
2) Diameter (mm)	12.10	12.10	12.10
3) Weight variation	2.05	2.60	1.75
4) Hardness (kg/cm^2)	4.5	4.5	4.0
5) Disintegration Time (min)	12.10	10	8
6) Friability (%)	0.78	0.81	0.88
7) Content Uniformity	93.70±1.50	91.86±4.5	95.57±3.36
8) Cum.% Drug Released	73.05	61.65	81.11

CONCLUSION.

Results indicate that formulations prepared by the technique of solid dispersion showed increase in the dissolution of Poorly water soluble drug.

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