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Formulation and evaluation of fast dissolving tablets of Flurbiprofen

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ABSTRACT

The present research work was to formulate FDT of already used therapeutic molecule to enhance effectiveness, and to avoid side effects (gastric irritation) of the drug. Flurbiprofen is non-steroidal anti-inflammatory drug; mainly used for osteoarthritis and rheumatoid arthritis. Solid dispersions were evaluated by solubility study, drug content, in-vitro drug release study, dissolution efficiency and characterized by FT-IR. Fast Dissolving Tablets of Flurbiprofen was prepared by direct compression by addition of superdisintegrant like Sodium starch glycolate, Crosscarmallose sodium, and Crospovidone and by effervescence technology. Stability study confirms there is no change in hardness, friability, disintegration time, and drug content and *in-vitro* drug release pattern. Among all formulations, F15 containing 5% w/w of Crospovidone is least disintegration time 25.68 sec and release 99.55% of drug in 20 min.

Keywords: Flurbiprofen, Solid dispersion, fast dissolving Tablet, Stability Study.

INTRODUCTION

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, and patient compliance. Drug absorption is defined as the process of movement of unchanged drug from the site of administration to systemic circulation [1]. The drug that has a high aqueous solubility the dissolution rate is rapid the rate at which the drug crosses or permeates cell membrane is the slowest or rate limiting step [2, 3].

SOLID DISPERSIONS:

Solid dispersion technology is the science of dispersing one or more active ingredients in an inert matrix in the solid stage in order to achieve increased dissolution rate, sustained release of drugs, altered solid state properties, enhanced release of drugs from ointment and suppository bases, and improved solubility and stability [4].

FAST DISSOLVING TABLETS:

The development of new drug delivery systems for already existing drugs, with enhanced efficacy and bioavailability, thus reducing the dose and dosing frequency to minimize the side effects [8].

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance [9]. The most popular dosage forms being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow [10].

The difficulty is experienced in particular by pediatric and geriatric patients, but it also applies to people who are ill in bed and especially those who have no access to water and also in following conditions like: Parkinsonism, Motion sickness, Unconsciousness and Mentally disabled persons [11].

To fulfill these medical needs, the pharmaceutical technologists have developed a novel type of dosage form for oral administration, the Fast Dissolving Tablets (FDT), tablets that disintegrate and dissolve rapidly in saliva without water.

Flurbiprofen, a propionic acid derivative, is a nonsteroidal anti-inflammatory agent (NSAIA) with antipyretic and analgesic activity. Oral formulations of flurbiprofen may be used for the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. Flurbiprofen, a nonsteroidal anti-inflammatory agent (NSAIA) of the propionic acid class, is structurally and pharmacologically related to fenoprofen, ibuprofen, and ketoprofen, and has similar pharmacological actions. Flurbiprofen exhibits anti-inflammatory, analgesic, and antipyretic activities.

MATERIALS AND METHODS

Materials:

Flurbiprofen were gifted from the Spectrum pharma lab Hyderabad. AC-DI-SOL, Sodium Starch Glycolate, and Croscopvidone were purchased from M/S Healer's Lab Pvt. Ltd., Baddi. Sodium bicarbonate, Magnesium Sterate, Talc, Sodium Hydroxide, Sodium Phosphate, PVG-6000 were purchased S.D. Fine Pvt. Ltd., Mumbai. Methanols LR, Acetone LR, were purchased from S.D. Fine Chem. Ltd., Mumbai.

Methods:

Evaluation of physical mixtures of solid dispersions:

The prepared physical mixtures and solid dispersions were evaluated for solubility studies, percent drug content, dissolution efficiency, *in-vitro* drug release and Fourier transform infrared (FTIR), Differential scanning calorimetry (DSC), X-ray diffraction (XRD), scanning electron microscopy (SEM).

Determination of Solubility of Solid Dispersions:

Flurbiprofen solid dispersions equivalent to 10 mg of Flurbiprofen were added to 10 ml of Sorenson's buffer pH 6.8 in a 10 ml volumetric flask. The volumetric flasks were capped properly and shaken at 25⁰ and 37⁰ C in a temperature. Resultant samples containing undissolved solid dispersions suspended in the volumetric flask suitably diluted with Sorenson's buffer pH 6.8 and analyzed by UV

Determination of Drug Content:

Drug content was calculated by dissolving solid dispersions equivalent to 100 mg Flurbiprofen in 10 ml of methanol, filtered using 0.45µm Whatman filter paper, suitably diluted with Sorenson's buffer (pH 6.8) and analyzed by using UV spectrophotometer

In-vitro Drug Release:

Accurately weighed preparations equivalent to 100 mg of Flurbiprofen were added to 900 ml of dissolution medium in USP II Paddle type apparatus and stirred at speed of 50 rpm. The collected samples were analyzed after filtration and dilution at 247 nm using UV-visible spectrophotometer.

Fourier Transform infrared spectroscopy:

Fourier Transform Infrared spectra were recorded on samples prepared in potassium bromide (KBr) disks.

The scanning range was 400 to 4000 cm⁻¹ and the resolution was 4 cm⁻¹.

RESULTS AND DISCUSSION

The drug content of physical mixtures (FP1-FP3 & FPG1-FPG3) and solid dispersions (FPVP1-FPVP3 & FPEG1-FPEG3) was found to be from 97.94 to 99.37, which is found to be within the range of ±1 % of the theoretical claim which shows the uniformity and reproducibility of the obtained method. The saturation solubility of pure drug, PM and SD was found to be 0.014mg/ml, 0.228mg/ml to 0.711mg/ml and 0.252 mg/ml to 0.894 mg/ml.

The *in-vitro* release profile of Flurbiprofen of PVP K30 physical mixtures, Flurbiprofen of PEG-4000 physical mixture, and solid dispersions formulations FP1, FP2, FP3, FPG1, FPG2, FPG3, FPVP1, FPVP2, FPVP3, FPEG1, FPEG2 and FPEG3 are shown and the graph for the comparison of the cumulative percent release is illustrated. In all the cases, cumulative percent release was much greater than pure Flurbiprofen. It is apparent from the Table and the Figure that as the percent of carrier (PVP K30 & PEG-4000) is increased the dissolution rate. Pure Flurbiprofen yield the low release due to its hydrophobic property causing the powder to float on the surface of the dissolution media and prevented its surface to make contact with medium for initial time intervals.

CONCLUSION

The data obtained from the study of "Formulation and evaluation of fast dissolving tablets of Flurbiprofen" reveals following conclusion:

Solid dispersions were evaluated for solubility, percent drug content, dissolution efficiency, *in-vitro* drug release studies and drug polymer interaction studied by FT-IR. Formulations containing Flurbiprofen-PVP K30 solid dispersions in 1:3 ratio (FPVP3) showed better dissolution rate, dissolution efficiency. And on the basis of *in-vitro* release formulation (FPVP3) was chosen for

Evaluation of Solid Dispersion: Determination of Solubility of Solid Dispersion:**Table 1: Solubility data of Flurbiprofen, physical mixture and solid dispersion in Sorenson's buffer pH 6.8 at 25⁰C and 37⁰C.**

Formulation code	Flurbiprofen solubility (mg/ml) at 25 ⁰ C	Flurbiprofen solubility (mg/ml) at 37 ⁰ C
Pure Drug	0.014333 ± 0.003086	0.018417 ± 0.001809
FP1	0.28825 ± 0.002883	0.316167 ± 0.00527
FP2	0.383333 ± 0.002765	0.438917 ± 0.001665
FP3	0.46675 ± 0.003	0.564917 ± 0.002082
FPG1	0.2275 ± 0.002537	0.251833 ± 0.001507
FPG2	0.331 ± 0.002634	0.388333 ± 0.001127
FPG3	0.444917 ± 0.004856	0.501083 ± 0.001127
FPVP1	0.533083 ± 0.002126	0.603833 ± 0.001258
FPVP2	0.6775 ± 0.002537	0.751 ± 0.001146
FPVP3	0.803833 ± 0.003263	0.894417 ± 0.000878
FPEG1	0.481333 ± 0.00366	0.575333 ± 0.001127
FPEG2	0.620167 ± 0.006385	0.715417 ± 0.008098
FPEG3	0.71125 ± 0.005074	0.80475 ± 0.00522

Data are expressed as mean ± S.D. (n = 3)

ESTIMATION OF DRUG CONTENT:**Table 2: Percent Drug Content of Flurbiprofen-PVP K-30 & Flurbiprofen-PEG-4000 Physical Mixtures and Solid Dispersions**

SR.NO.	Formulation Number	%Drug Content
1	FP1	99.08333±0.242813
2	FP2	98.66667±0.438986
3	FP3	98.25±0.450694
4	FPG1	99.025±0.15
5	FPG2	98.10833±0.448144
6	FPG3	98.08333±0.401819
7	FPVP1	99.36667±0.500208
8	FPVP2	98.61667±0.58648
9	FPVP3	98.51667±0.57027
10	FPEG1	98.91667±0.496446
11	FPEG2	97.94167±0.312583
12	FPEG3	98.08333±1.127035

Data are expressed as mean ± S.D. (n = 3)

Figure 1: Solubility of Flurbiprofen, physical mixture and solid dispersion in Sorensen's buffer pH 6.8 at 25°C and 37°C.

Figure 2: Percent Drug Content of Flurbiprofen-PVP K-30 & Flurbiprofen-PEG-4000 Physical Mixtures and Solid Dispersions

IN-VITRO DISSOLUTION STUDIES:**Table 3: Dissolution Release Profile of Flurbiprofen from Physical Mixture.**

Time (min)	Cumulative Mean Percent Drug Release $\pm$ Standard Deviation						
	Pure drug	FP1	FP2	FP3	FPG1	FPG2	FPG3
0	0	0	0	0	0	0	0
5	1.89	5.265	10.2	14.1075	4.38	8.8725	12.03
	± 0.2025	± 0.2475	± 0.225375	± 0.2475	± 0.213849	± 0.202916	± 0.213849
10	3.7071	12.73335	19.52633	26.19818	12.27487	17.46986	25.08587
	± 0.259056	± 0.225649	± 0.214098	± 0.214124	± 0.236576	± 0.225225	± 0.236576
15	6.028717	20.18749	26.68052	34.46977	20.531	29.07676	33.82123
	± 0.236852	± 0.225898	± 0.225862	± 0.237562	± 0.24834	± 0.225475	± 0.236839
30	13.92541	34.4374	42.73013	50.86552	37.80379	43.16403	50.43376
	± 0.237114	± 0.226148	± 0.226112	± 0.248275	± 0.237114	± 0.248564	± 0.225763
45	24.35837	44.66062	53.42753	62.36694	49.23825	54.54443	61.43971
	± 0.237376	± 0.237364	± 0.226358	± 0.214898	± 0.214885	± 0.237339	± 0.21486
60	34.2854	52.37515	61.87928	70.82108	54.94037	62.32241	67.83783
	± 0.226673	± 0.248788	± 0.226609	± 0.237626	± 0.215123	± 0.237601	± 0.20375

Data are expressed as mean $\pm$ S.D. ($n = 3$)**Table 4: Dissolution release profile of Flurbiprofen from solid dispersion**

Time (min)	Cumulative Mean Percent Drug Release $\pm$ Standard Deviation					
	FPVP1	FPVP2	FPVP3	FPEG1	FPEG2	FPEG3
0	0	0	0	0	0	0
5	7.29	23.2725	36.465	9.93	16.59	25.02
	± 0.225	± 0.202916	± 0.213849	± 0.236339	± 0.236339	± 0.225
1	18.6156	38.98836	57.04802	23.62853	30.94093	45.3203
0	± 0.22525	± 0.214074	± 0.248077	± 0.248103	± 0.236602	± 0.22525
1	28.70128	54.93165	74.11386	34.62728	43.74029	60.09313
5	± 0.203415	± 0.203379	± 0.236852	± 0.236877	± 0.214373	± 0.203415
3	49.23813	75.73761	90.71859	54.96821	66.06383	78.79731
0	± 0.248564	± 0.172529	± 0.248615	± 0.248641	± 0.214611	± 0.248564
4	61.69028	85.75162	99.81168	68.0492	75.34713	88.3347
5	± 0.214848	± 0.130698	± 0.172872	± 0.237415	± 0.226	± 0.248839
6	70.81119	93.16666	-	74.41716	82.78815	94.59759
0	± 0.226238	± 0.226		± 0.226338	± 0.22625	± 0.249115

Data are expressed as mean $\pm$ S.D. ($n = 3$)

Figure-3: Cumulative Percent Release of Flurbiprofen from Physical Mixtures of Flurbiprofen-PVP K-30 and Flurbiprofen-PEG-4000 Systems

Figure 4: Cumulative Percent Release of Flurbiprofen from Solid Dispersions of Flurbiprofen-PVP K-30 and Flurbiprofen-PEG4000 Systems

FT-IR STUDY:

Figure-5 FT-IR Spectra of PVP K 30.

Figure-6 FT-IR Spectra of PEG 4000

Figure 7: Zero Order Dissolution Release Profile of Flurbiprofen from F1-F5

Figure 8: Zero Order Dissolution Release Profile of Flurbiprofen from F6-F10

Figure 9: Zero Order Dissolution Release Profile of Flurbiprofen from F11-F15

Figure 10: Zero Order Dissolution Release Profile of Flurbiprofen from F15-F20.

FDT. Fast dissolving tablets were prepared by adding different concentrations (1-5%) of superdisintegrants and by effervescent technology. The disintegration time of all the formulations were found between 25.68 ± 1.41 to 134.22 ± 5.16 secs. The *in-vitro* wetting time of all the formulations were varied between 27.45 ± 1.40 to 125.66 ± 5.76 secs. The dispersion time of all formulation were varied between 30.91 ± 1.68 to 142.71 secs. Drug content of all formulation varied from 48.65833 ± 0.146487 to 50.54167 ± 0.052042 mg per tablet. The order of drug release **F15>F20>F14>F10>F13>F5>F19>F9>F4>F12>F3>F8>F18>F11>F2>F17>F16>F7>F1.**

Stability study for F4, F10, F15 and F18 were performed at temperatures ($40^\circ\text{C}/75\%\text{RH}$). All the formulations showed no significant variation in all the parameters evaluated under the test period condition. From the above studies it was concluded that the F15 is best formulation for Fast Dissolving Tablets of Flurbiprofen.

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