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Formulation, Development and Evaluation of Bilayer Tablet of Flurbiprofen

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ABSTRACT
In the Study of Formulation of Bilayer Tablet of Flurbiprofen the Following Materials Using sodium starch glycolate as immediate release and HPMC K15 in different ratios as release retardant materials using a wet granulation method. All tablets exhibited good physical properties with Respect to appearance, content uniformity, hardness, weight variation and *Invitro* dissolution data show at increasing proportions Of sodium starch glycolate for immediate release whereas HPMC K15sustaineddrugreleaserate. The bilayer tablets showed an initial release of drug In about1hr, then sustaining the release for 12h, The kinetic analysis of dissolution data showed that release was observe din these tablets. When data was fitted to the Higuchi model. Bilayer tablets of flurbiprofen can be successfully formulated Using sodium starch glycolate and HPMC K15 in different ratios as release retardant materials employing a wet granulation method.

Keywords : Sodium Starch Glycolate, HPMC K15, Wet Granulation Method.

I. INTRODUCTION

Bilayer tablet is suitable for sequential release of two drugs in combination, separate two incompatible substances and also for sustained release tablet in which one layer is immediate release as initial dose and second layer is maintenance dose. Bilayer tablets have been developed to achieve controlled delivery of different drugs with pre defined release profiles. In the last decade interest in developing a combination of two or more API's in a single dosage form has increased in the pharmaceutical industry, promoting patient convenience and compliance. Several pharmaceutical companies are presently developing bi-layer tablets, for a variety of reasons patent extension, therapeutic, marketing to name a few.[1] Incertin conditions drug treatment may be advantageous to be delivered in a biphasic manner rather than a single phase extended release preparation. In the first phase of drug release, the immediate release dose fraction (also called loading-dose) reaches a therapeutic drug level in the blood plasma quickly after administration, while the second extended release phase (called the maintenance- dose) provides the dose fraction, required to maintain an effective the rapeutic level for a prolonged period. Examples of such systems can be founds bilayer tablets, drug layered matrices or combinations of immediate and extended release multi particulates.

II. METHODS AND MATERIAL

Chemicals:
Flurbiprofen were purchased from aarti Pharmaceuticals Pvt. Ltd. Mumbaisodium starch glycolate, (Research grade were purchased from loba chem.)HPMC K15 purchased from color on lab, Starch, Pvp-k-30, Microcrystalline Cellulose, Lactose

fraction, required to Talcum and Magnesium Stearate.

	Batches					
Ingredients	**IR 1**	**IR 2**	**IR 3**	**IR 4**	**IR 5**	**IR 6**
Flurbiprofen	50	50	50	50	50	50
Crosscarmellose	2	6	10	---	---	---
Sodium Starch Glycolate	---	---	---	2	6	10
Lactose	148	144	140	148	144	140
Pregelitinised starch solution	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	q.s	q.s	q.s	q.s	q.s	q.s
Talc	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	200	200	200	200	200	200

Formulation of Preliminary batches of FB Immediate Release layer (IR1-IR6)

The composition of preliminary batches of immediate release layer is given in the following table. The ingredients viz. flurbiprofen, croscarmellose / sodium starch glycolate and lactose monohydrate were mixed in mortar and pestle in geometrical manner. Aqueous wet granulation method was used for the preparation of IR layer. Pregelitinised starch was used as the binder. 5% starch paste was prepared using water. This paste was added in the above mixture of ingredients in sufficient quantity to obtain wet mass. This wet mass was then passed through sieve no. 16 to obtain the granules. These granules were then dried at 60° C. Dried granules were then passed through sieve no 40 to gain fines. The granules were lubricated with talc and magnesium stearate. Calculated amount of fines were then added to granules and mixed. The granules were punched on single punch tablet press tablet machine with final weight of tablet as 200 mg.

Table 2 : composition of preliminary trial Batches.

	Batches					
Ingredients	**SR1**	**SR 2**	**SR3**	**SR4**	**SR5**	**SR6**
Flurbiprofen	50	50	50	50	50	50
HPMC K15				2	6	10
Xanthum Gum	2	6	10	---	---	---
MCC	148	144	140	148	144	140
PVP K30 solution	q.s	q.s	q.s	q.s	q.s	q.s
Magnesium stearate	q.s	q.s	q.s	q.s	q.s	q.s
Talc	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	200	200	200	200	200	200

Fourier transformed infrared (FTIR) spectroscopy

The KBr dispersion pellet of the given sample of Flurbiprofen, sodium starch glycolate and HPMC K15M were prepared and scanning was done by using Shimadzu IRSpectrophotometer at SAIF, Chandigarh, India. The spectrum obtained has wellresolved peaks, which ascertained the purity of the sample of all three drugs. The sampleIR spectrum was interpreted & matched with reference IR spectra, which infers that thecompound contains all the peaks to be obtained as authentic sample of drugs.

UV Spectroscopy:

Accurately weighed drug (100 mg) was transferred to a 100 ml volumetric flaskand dissolved in and diluted to 100ml with, water, 6.8 phosphate bufferseparately. Final standard stock solution of 100µg/ml was prepared by diluting 10 ml ofthe above solution to 100ml with respective solutions. The standard stock solutions ofFlurbiprofen scanned in the range of 200 to 400 nm against, water, 6.8phosphate buffer. Maximum absorbance was obtained at 247 nm in all solutions.

Calibration curves were plotted over a concentration range of 2-20 µg/ml. accurately measured standard stock solutions (0.2, 0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 ml) were transferred to a separate series of 10 ml volumetric flasks. The volume was adjusted to the mark with 0.1 N HCL, water, 6.8 phosphates buffer separately and mixed. The absorbance of each solution was measured at 247 nm against water, 6.8 phosphate buffer as a blank respectively. Calibration curves were constructed by plotting absorbance versus concentrations at 247 nm wavelength. Each reading was an average of three determinations.

In-vitro Release Studies:

The in-vitro dissolution study of all the batches Flurbiprofen was carried out using USP II (Paddle) dissolution apparatus. The test was performed using 900ml of pH 6.8 phosphate buffer at 50 rpm and 37±0.5 °C. The samples (5 ml) of the solution were withdrawn at each specified time intervals and the sink condition was maintained by transferring 5 ml of fresh dissolution media each time of the sample withdrawal. The samples were diluted with same media if needed then analyzed at 247 nm using UV-Visible spectrophotometer.

Release Kinetics:

To study the mechanism of drug release from the sustained release matrix tablet, the in vitro drug release data were fitted to various kinetic models like zero order as cumulative amount of drug release v/s time, First order as log cumulative % of drugremaining v/s time, Hixson-Crowell, Higuchi as cumulative % of drug release v/s square root of time and K-Peppas equation and coefficient of correlation (r) values were calculated for linear curves by regression analysis of the above plot.This study was done by using microsoft excel. These models used to explain drug release mechanism of the tablet release.

III. RESULTS AND DISCUSSION

DRUGEXCIPIENTSCOMPATIBILITY STUDY
IR study of drug:

FTIR spectra of flurbiprofen and showed the same absorption pattern as the combination of drugs and excipients of formulations.

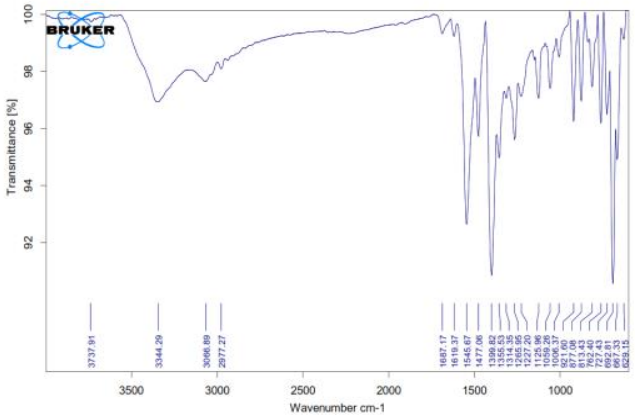

Fig.1 : IR of Flurbiprofen

Table 3. IR Interpretation of Flurbiprofen

Sr.no	Funtional group	Reported range	Observed range
1	C-F(fluorin group)	1000-1400	1125.96
2.	-OH (acid)	3300-3600	3344.25
3.	-CO(acid)	1705-1720	1687.17
4.	CH_3(methyl group)	1450-1375	1355.53
5.	C=C	1500-1600	1545.67

Preformulation and Post formulation Results:

All pre formulation parameters were applied. Bulk density and tapped density are two of the most important studies to be done before the development of formulation. Bulk density, angle of repose, compressibility index, hausner's ratio, moisture content and tapped density were checked by adopting the standard methods as described in USP. Results are shown in. These values were in acceptable range.

Table 4. Precompression parameters of FB IR layer (IR1-IR6)

parameters	IR1	IR2	IR3	IR4	IR5	IR6
Weight variation (mg)	198±1.2	201±1.5	199±1.3	198±0.8	199±0.8	200±0.9
Hardness (kg/cm²)	5.1±0.2	4.9±0.1	5.2±0.3	5.2±0.1	5.2±0.1	5.0±0.3
% Drug content	98.4	99.1	97.5	99.4	99.4	98.6
Disintegration time (min)	8.42±0.42	6.22±0.28	3.41±0.49	6.48±0.35	6.48±0.35	2.58±0.36

Table 5. Post-compression study of FB IR layer (IR1-IR6)

Time (min)	IR1	IR2	IR3	IR4	IR5	IR6
2	11.81±0.81	12.6±0.51	14.17±0.25	15.86±0.35	18.11±0.85	16.98±0.12
5	35.43±0.63	40.61±0.70	44.88±0.52	46.35±0.58	44.7±0.49	44.1±0.42
10	45.11±0.97	45.22±0.92	58.27±0.41	60.07±0.42	63.11±0.41	62.32±0.98
15	57.93±0.48	60.75±1.1	69.07±0.52	67.38±0.47	75.48±0.27	76.61±0.73
30	66.48±0.72	68.73±0.48	78.63±0.85	78.9±0.28	87.52±0.95	85.6±0.43
45	76.61±0.61	78.52±0.57	80.32±0.25	87.86±0.35	90.45±0.71	89.1±0.49
60	83.36±0.90	86.4±0.85	88.98±0.75	95.73±0.84	98.55±0.75	97.9±19

Table 6. % Cumulative drug release of preliminary batches of FB IR layer (IR1-IR6)

Parameters	SR1	SR2	SR3	SR4	SR5	SR6
Angle of Repose	30.45	29.45	28.44	28.00	32.25	27.65
Bulk density (gm/ml)	0.43	0.42	0.41	0.40	0.49	0.42
Tapped density (gm/ml)	0.50	0.48	0.47	0.46	0.57	0.45
Carr's	12.4	12.11	12.60	12.26	12.71	12.25
Hausner	1.14	1.148	1.144	1.14	1.150	1.139

Table 7. Pre-compressional parameters of preliminary batches of FB SR layer.

parameters	SR1	SR2	SR3	SR4	SR5	SR6
Weight variation (mg)	198±1.2	197±1.5	199±1.3	198±0.8	200±1.5	200±0.9
Hardness (kg/cm²)	6±0.2	6.5±0.1	5.5±0.3	6.2±0.1	6±0.2	5.0±0.3
% Drug content	97.4	98.1	98.5	98.4	98.9	96.6
Disintegration time (min)	2.42±0.42	6.22±0.28	3.41±0.49	6.48±0.35	6.12±0.24	8.58±0.36

Table 8. Post-compressional parameters preliminary batches of FB SR layer (SR1-SR6).

Time (hrs.)	SR1	SR2	SR3	SR4	SR5	SR6
0.5	4.05±0.81	5.4±0.42	7.6±0.84	15.4±0.25	19.23±0.45	16.58±0.21
1	7.9±0.72	9.9±0.36	11.8±0.61	23.3±0.24	32.06±0.72	24.97±0.42
2	12.37±0.41	13.16±0.52	16.65±0.67	35.4±0.74	39.03±0.4	30.48±0.18
3	22.9±0.32	24.07±0.35	32.06±0.72	43.5±0.41	48.48±0.21	45.56±0.27
4	30.15±0.65	31.6±0.14	37.34±0.41	45.4±0.12	56.02±0.34	51.32±0.45
5	35.43±0.48	36.9±0.28	46.46±0.52	55.4±0.46	62.7±0.32	59.28±0.38
6	43.98±0.71	46.9±0.41	48.03±0.24	65.4±0.52	70.65±0.41	66.48±0.11
7	45.56±0.52	55.8±0.37	57.82±0.41	76.1±0.37	79.98±0.28	76.95±0.32
8	56.7±0.25	57.03±0.42	61.65±0.52	78.6±0.56	87.86±0.37	87.3±.22
9	61.65±0.74	62.77±0.48	69.18±0.48	87.4±0.42	92.02±0.16	90.33±0.37
10	65.92±0.36	70.65±0.52	75.48±0.32	93.4±0.43	97.65±0.24	95.28±0.32

Table 9. % Cumulative drug release of preliminary batches of FB SR layer (SR1-SR6)

IV. CONCLUSION

In the present work, the incorporation of Flurbiprofen, an anti-inflammatory agent was performed in inert HPMC K 15 and Sodium Starch Glycolate. where sodium starch glycolate is used as super disintegrating agent and HPMC K 15and polymer in different concentration is used to achieve sustained release kinetic for drug. There was no chemical interaction between the drug and polymers as inferred primarily from DSC and FTIR .Thus by Hydroxyl propyl methyl cellulose proved useful as arate controlling polymer to produce a controlled release formulation of Flurbiprofen using the dissolution controlled mechanism. The prepared optimized bi-layer tablet formulation of flurbiprofen was stable. Hence, this optimized bi-layer dosage form could be a potential formulation for delivery of drugs from a single dosage form could be potential formulation for delivery of drug from single dosage from could be improve patient compliance and give better disease management.

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