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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLET OF FLUPIRTINE MALEATE

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ABSTRACT

The objective of this present study was to design bilayer tablet of Flupirtine Maleate for biphasic release and *in vitro* evaluation of the same. Bilayer tablets comprised two layers, i.e. immediate release and Sustained release layer. The immediate release layer comprised crosspovidone as a super disintegrant and the Sustained release layer comprised HPMC K100M and HPMC K4M as the release retarding polymers. Direct compression method was used for formulation of the bilayer tablets. *In vitro* dissolution studies were carried out in a USP apparatus I, basket method. HPMC K100M and HPMC K4M Sustained the release of drug from the Sustained release layer for 24 hr. FTIR studies revealed that there was no interaction between the drug and polymers used in the study. The release of Flupirtine Maleate was found to follow a pattern of Higuchi model, indicating the drug release by diffusion controlled. Accelerated stability studies were carried out on the prepared tablets in accordance with ICH guidelines. There were no changes observed in physicochemical properties and drug release pattern of tablets. Biphasic drug release pattern was successfully achieved through the formulation of bilayer tablets in this study for improve patient compliance and give better disease management.

Keywords: Sustained release, Flupirtine Maleate, Biphasic release, Polymers HPMC K4M and HPMC K100M and Crosspovidone.

INTRODUCTION

The aim of this investigation is to Formulate and Evaluate the Sustained release Bilayer tablets of Flupirtine Maleate using different synthetic polymers. The concept of Bilayer tablet technology is utilized to develop sustains release and immediate formulation for a single drug or combination of drugs. Bilayer tablets are preferred in some cases because they maintain uniform drug levels, reduce dose, side effects, increase the safety margin for high-potency drugs and thus offer better patient compliance Flupirtine is an amino pyridine that functions as a centrally acting non-opioid, non-steroidal analgesic. It is a selective neuronal potassium channel opener that also has NMDA receptor antagonist properties. Its muscle relaxant properties make it popular for back pain and other orthopedics uses and it is also used for migraines, in oncology, postoperative care, and gynecology, and its neuro-protective properties make it for possible use in Creutzfeldt- Jakob disease, Alzheimer's disease, and multiple sclerosis. Flupirtine Maleate possess short biological half life (6.5hrs), patient should go for frequent administration usually four times a day which might be a risk to the patient. In order to overcome this, Flupirtine Maleate sustained release dosage forms are formulated **[1,12]**

Flupirtine Maleate which is used as an analgesic is formulated as bilayered tablet which comprises of two layers among which the first layer is immediate release layer to provide immediate relief from pain and the second layer is sustained release layer to maintain steady state concentrations of drug in the blood. The current research is to formulate and evaluate an ideal bilayer matrix tablet of sustained release profile by using suitable methods by using different polymers.

MATERIAL AND METHODS

Flupirtine Maleate, obtained lupin pharma ltd pithampur indore . HPMCK100M, HPMC K4M, Cross povidone, Magnesium stearate, Micro Crystelline Cellulose, Talc, Sodium hydroxide pellets, Potassium dihydrogen phosphate. All other excepients obtained from Loba Chemicals, Mumbai and National Chemicals, Vadodara.

Formulation of immediate release layer

The tablets were prepared by direct compression technique. Before blending of drug and other excipients, they were sifted through sieve no. 40 to remove any large particles. Drugs and other excipients were blended for 10 minutes. Then, subsequently this powder mixture was blended for 5 minutes with talc. This mixture was directly compressed to get the tablets. The final weight of immediate release layer fixed to 200 mg ·[12]

Formulation of sustained release layer

By direct compression method and follow steps as immediate release layer .

Table 1: Composition of IR layer of bilayer tablet of Flupirtine maleate

Immediate release layer	
Ingredients	**Quantity per tablet(mg)**
Flupirtine Maleate	100
Crosspovidone	10
Microcrystelline cellulose	86
Magnesium stearate	2
Talc	2

Table 2: Composition of SR layers of bilayer tablet of Flupirtine maleate

Composition (mg)	**Formulation code**								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Flupirtine Maleate	320	320	320	320	320	320	320	320	320
HPMC K4M	40	40	40	60	60	60	80	80	80
HPMC K100M	60	80	100	60	80	100	60	80	100
Microcrystelline cellulose	95	75	55	75	55	35	55	35	15
Megnecium stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Total weight	520 mg								

Drug–excipient compatibility studies: A Compatibility study focuses on a binary mixture of drug substance and some selected excipients in a fixed ratio with or without added moisture. The mixture stored at elevated temperatures as 40ºc 75%RH, 55ºC 60%RH in capped vials. The result of the interaction between the active drug and excipients is determined by FTIR.

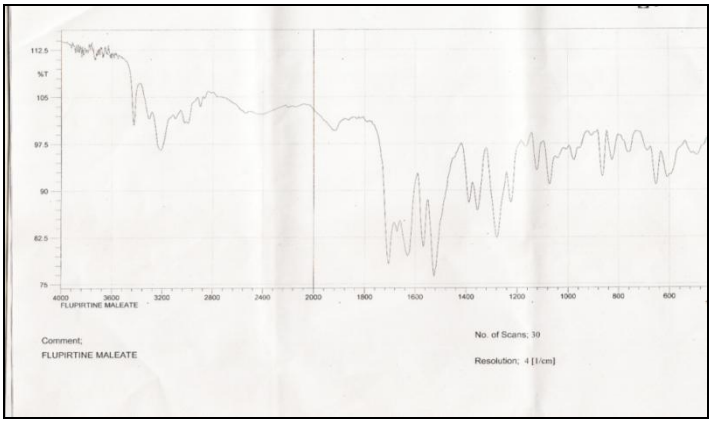

Fig. 1: IR spectra of Drug Flupirtine Maleate

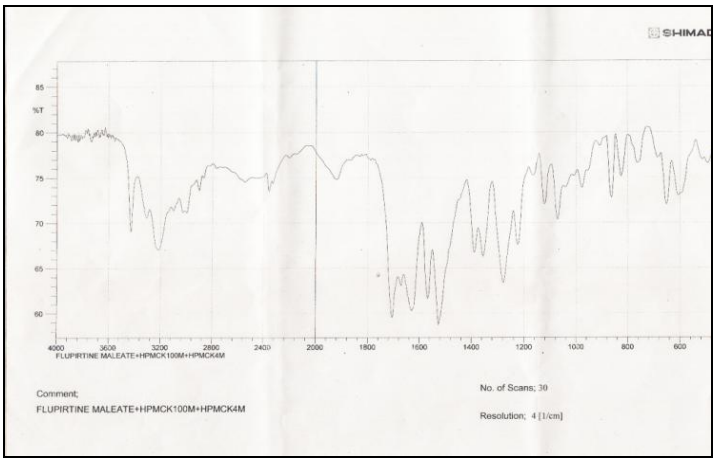

Fig. 2: IR spectra of mixture of Flupirtine Maleate and HPMCK100M +HPMCK4M

Table 4: Evaluation of Sustained Release Bilayer Tablet of Flupirtine Maleate

Formulation	Hardness (kg/cm^2)	Wt. variation (mg)	Thickness (mm)	% Fribility	*In-vitro* disintegration time(sec.)
F1	7.2±0.32	720.8±3.12	7.32±0.15	0.73±0.23	36.13±3.26
F2	6.91±0.19	722.1±2.15	7.49±0.22	0.74±0.18	29.24±4.76
F3	7.0±0.15	±721.7±2.43	7.45±0.19	0.74±0.15	28.68±2.48
F4	7.16±0.36	720.9±2.32	7.39±0.26	0.73±0.42	32.82±3.27
F5	6.8±0.42	719.8±1.98	7.53±0.23	0.75±0.32	28.95±2.56
F6	7.4±0.21	718.6±2.11	7.21±0.13	0.72±0.29	39.78±3.22
F7	7.1±0.24	721.1±4.56	7.38±0.21	0.73±0.11	30.63±2.43
F8	6.8±0.18	720.8±3.18	7.62±0.33	0.81±0.25	28.89±4.63
F9	7.4±0.25	720.8±4.078	7.50±0.241	0.74±0.063	28.16±1.48

Preformulation studies

Colour and nature: Transferred small quantity of the sample on a white piece of paper, spreaded the powder and examined visually.

Taste and odour: Very less quantity of Flupirtine Maleate was used to get taste with the help of tongue as well as smelled to get the odour **[4]**

Pre-compression characterization of blend

Bulk density: A known quantity of powder was poured into the measuring cylinder carefully level the powder without compacting, if necessary and read the unsettled apparent volume. Calculate the bulk density, in gm per ml, by the formula**.[5]**

Tapped density: Tapped density is the ratio of mass of powder to the tapped volume.

Angle of repose: It is defined as the maximum angle is possible between the surface of the pile of the powder and the horizontal plain.[5]

Compressibility Index: The compressibility Index is measures of the propensity of powder to be compressed.

Hausner Ratio: It is the ratio of volume of tapped volume or tapped density to bulk density.

Evaluation of bilayer tablet

Hardness: Tablet hardness has been defined, as the force required breaking a tablet a diametric compression test. Hardness was measured by hardness tester.

Friability test: Weighed amount of 20 dedusted tablets were subjected to rotating chamber of "Roche type friability tester". **[5]**

Disintegration time: Equivalent to 10mg of Flupirtine Maleate was accurately weighed from powdered bilayered tablets and it was dissolved in distilled water to form a clear solution.

1 ml of the sample was withdrawn, suitably diluted with pH 6.8 phosphate buffer respectively and analysed spectrophotometrically at λmax 250 nm respectively.[[6-8]].

In vitro dissolution Studies

For immediate release layer Dissolution rate was studied by using USP type-I apparatus at 75 rpm using 900ml of 0.1 N HCl solutions as dissolution medium. Temperature of the dissolution medium was maintained at 37±0.5°C, aliquot of 5 ml of dissolution medium was withdrawn at every 15 min interval the absorbance of solution was measured by UV spectrophotometric method at 250 nm and concentration of the drug was determined from standard calibration curve. The volume of the dissolution medium was adjusted to 900ml at every sampling time by replacing 5 ml with same dissolution medium **[21,7,6]**

The in vitro release of drug from sustained layer was carried out for 24 hours using basket type tablet dissolution apparatus USP type-I containing 900 ml of dissolution medium maintained at 37±0.5°C and speed of agitation at 75 rpm. Using 900 ml of pH 6.8 phosphate buffers as a dissolution medium. **[26,4,8]**

Table 5: Cumulative percent drug release data for bilayer tablet for Sustained release

S. No.	Time (hr)	Cumulative percent drug release								
		F1	F2	F3	F4	F5	F6	F7	F8	F9
1	0	0	0	0	0	0	0	0	0	0
2	1	29.23	22.47	23.766	28.18	26.11	30.78	31.63	29.23	26.44
3	2	33.45	31.68	34.53	35.96	34.86	38.55	36.41	34.27	33.34
4	3	38.22	42.43	41.65	45.19	46.46	47.61	41.47	42.65	41.19
5	4	46.13	49.68	48.48	54.12	53.91	52.81	48.99	46.89	44.87
6	5	52.78	58.34	55.32	60.27	59.38	58.37	53.64	49.77	48.70
7	6	60.49	59.26	58.82	66.86	65.67	63.16	59.53	54.12	52.25
8	7	69.231	64.12	62.57	68.23	68.98	67.39	64.59	57.32	56.87
9	8	78.852	68.27	69.95	74.48	72.26	71.36	69.27	62.36	61.63
10	9	85.106	79.54	74.52	76.96	75.93	78.23	73.78	68.40	64.93
11	10	92.176	91.38	82.98	82.32	80.87	81.52	79.29	75.58	70.17
12	11	95.39	92.25	8917	87.87	86.73	87.48	86.71	81.38	75.36
13	12	98.12	96.49	93.29	92.95	91.47	95.33	91.44	89.43	80.91
14	14	-	99.73	97.94	99.66	95	96.29	95.30	94.82	83.17
15	16	-	-	99.78	-	98.9	99.32	98.86	98.56	89.31
16	18	-	-	-	-	-	-	-	-	96.63

Table 3: Calibration curve for Flupirtine maleate in ph 6.8 at λmax 250 nm

S. No.	Concentration (µg/ml)	Absorbance (250 nm)
1	0	0
2	2	0.0682
3	4	0.1840
4	6	0.2551
5	8	0.3276
6	10	0.4230
7	12	0.5229
8	14	0.6296
9	16	0.7290
10	18	0.8265
11	20	0.9295

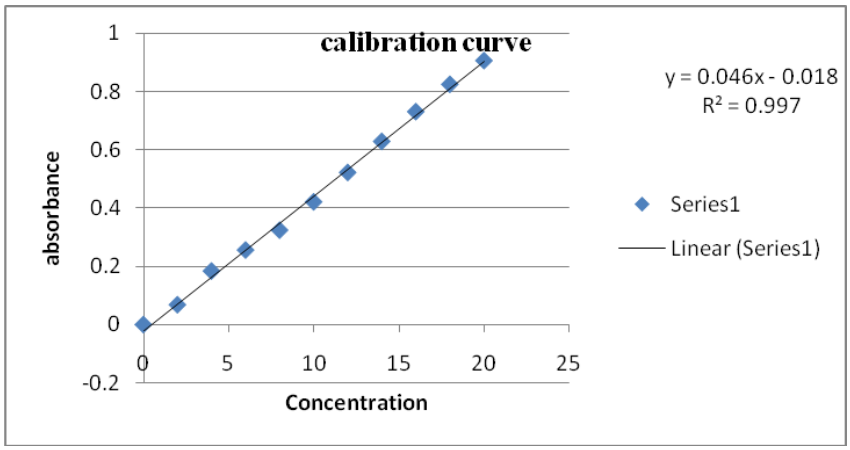

Fig. 3: Calibration curve of Flupittine Maleate in pH 6.8 buffer

RESULTS AND DISCUSSION

The present work was carried out on the Formulation and Evaluation of Sustained release Bilayer tablets of Flupirtine maleate comprising of immediate release layer for sudden onset of followed by Sustained release layer to maintain the steady state concentrations of the drug. HPMC K100M, HPMC K4M polymers were used in this investigation.

Calibration plots for Flupirtine Maleate shows good linearity indicating that selection of UV spectrophotometry method for estimation of above named drugs is correct.

The following parameters of bilayer tablets were within acceptable official IP limits Pre-compression parameters of bilayer tablets are Bulk density and tapped density for the formulations were in the range of 0.673- 0.761gm/ml and 0.831 - 0.894 gm/ml which indicated that passable flow properties. Compressibility index and Hauser's ratio were in the range of 14.80to 19.01 % and 1.17 to 1.23., indicated that excellent flow of powder blend.

The Evaluation of bilayer tablets (hardness, friability, weight variation, thickness, drug content, disintegration time) were within the acceptable official IP limits .The best formulation of bilayer tablets were selected for FTIR studies did not show any interaction between the polymer and pure drug. The results of *in-vitro* drug release profile of Bilayer tablets depicts that combinations of natural gums play important role in the retardation and optimization of the drug release and increases the retardation of drug release from the SR layer of a Bilayer tablet. All formulations were prepared for IR layer by using Crosspovidone, the percentage drug release shows formulations (F1-F9) in the range of 96.63% to 99.78% for F9 and F3.

The rate and mechanism of release of Flupirtine Maleate from the prepared bilayer tablets were analysed by fitting the dissolution data into the zero order, First order, Higuchi, Korsmeyer-Peppas and hexon crowel equations. All the Formulations (F1-F9) followed Zero order release Mechanism. Higuchi plots for all the formulations were linear indicating the drug release by diffusion controlled.

Table 6: R^2 Value of Drug release kinetics models of optimized formula F9

S. No.	Model	R^2Value
1	Zero order	0.926
2	First order	0.911
3	Higuchi	0.993
4	Hixon-crowell	0.972
5	Korsmeyer Peppas	0.987

The erosion model was applied to *in vitro* release data, the linearity was observed with r^2value and also Hixon-Crowell cube root model showed high r^2 value of 0.959 to 0.972 suggested that the geometrical shape of tablet diminished proportionality due to erosion of hydrophilic gel layer.

To explore the release pattern, results of the invitrodissolution data were fitted to the Korsmeyer-Peppas equation, which characterizes the transport mechanism. The value of release exponent (n) for all formulations were in between 0.478 to 0.689 indicates the non fickian transport or anomalous diffusion it refer to combination of both diffusion and erosion rate release.

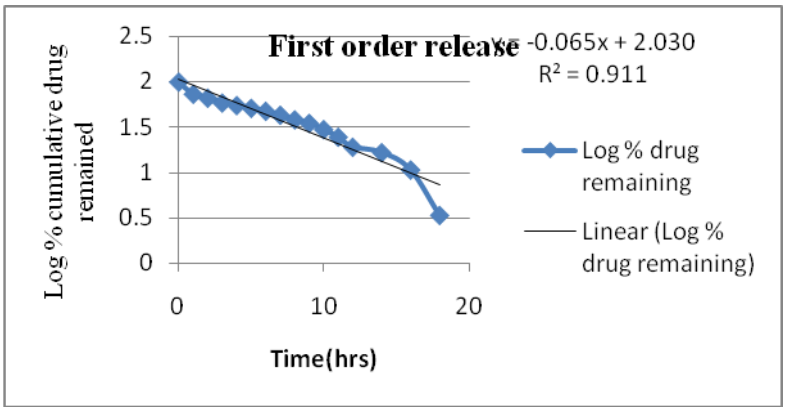

Fig. 4: First order drug release model of the optimized formulation F9

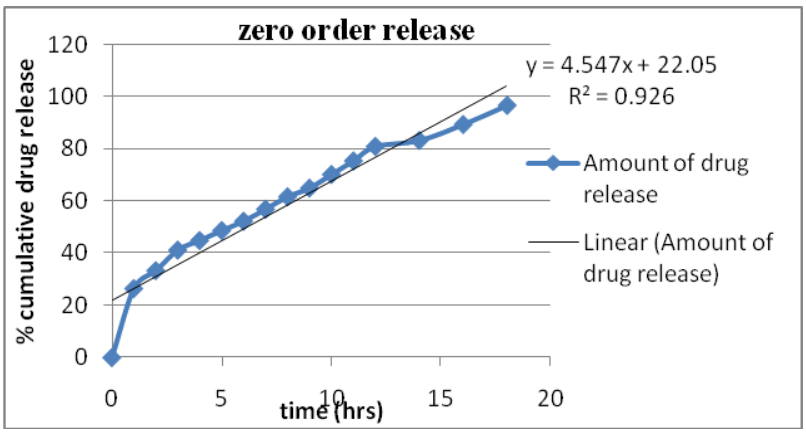

Fig. 5: Zero order drug release model of the optimized formulation

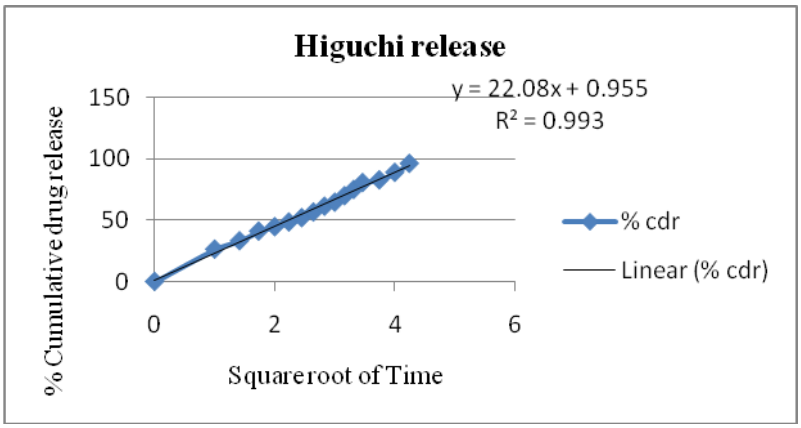

Fig. 6: Higuchi drug release model of the optimized formulationF9

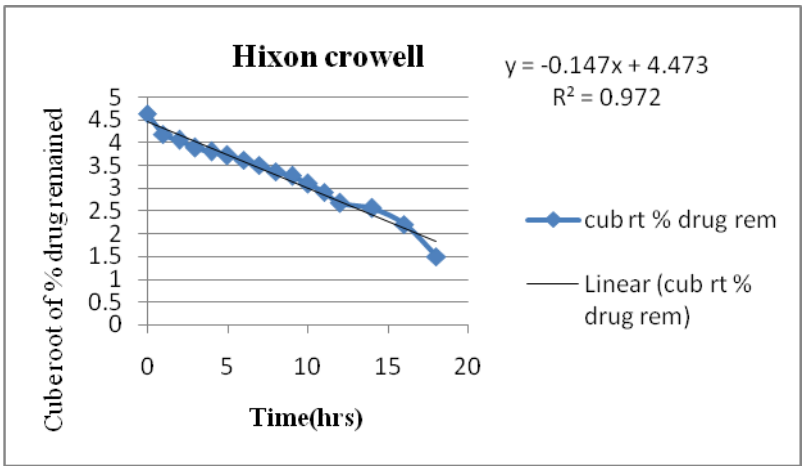

Fig. 7:.Hixon-Crowell model of the optimized formulationF9

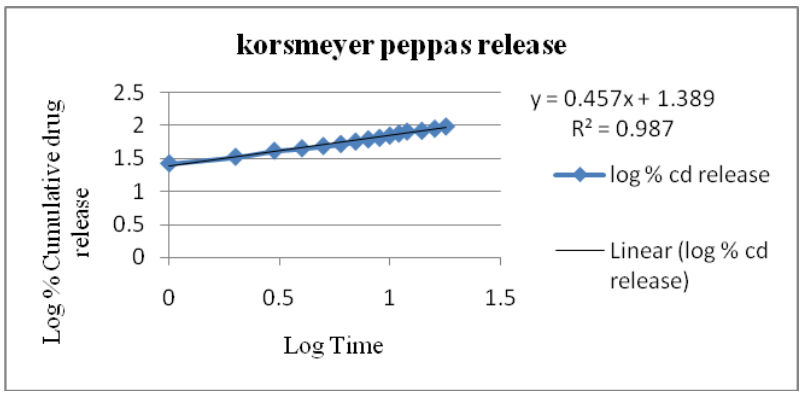

Fig. 8: Korsmeyer peppas drug release model of the optimized formulationF9

CONCLUSION

The present study was carried out to develop Sustained Release Bilayer Tablets of Flupirtine Maleate Immediate release layer and sustained release layer by direct compression method. Concluded that, the bilayer tablet technology can be successfully applied for Flupirtine Maleate using of polymers such as HPMC K100M, and HPMC K4M, can be used as rate controlling polymers by appropriate selection of the level of polymers in the Sustained release layer of Bilayer tablet. It can be concluded that the optimized batch F9 by adopting biphasic drug release pattern in a single dosage could improve patient compliance and give better pain mana gement.

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