International Journal of Advanced Pharmaceutical Sciences, Volume 1, Issue 08, Page 122-143
ISSN:2456-8147

FORMULATION AND EVALUATION OF SUSTAINED RELEASE BILAYER TABLET OF FLUPIRTINE MALEATE

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An open access journal

Supporting Information:

Received: 22 July 2018
Accepted: 31 July 2018
Published: 10 August 2018

Competing Interests:
The authors have declared that no competing interests exist.

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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.[1,2]

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.

Preparation of calibration curve :

100mg of Flupirtine drug was dissolved in required amount of pH 7.4 phosphate buffer and made up to 100ml , to give concentration 1000 µg/ml (primary stock solution). From the primary stock solution, 10 ml was taken and diluted to 100 ml with same buffer to give the concentration of 100 µg/ml (secondary stock solution), aliquots of 0.5 ml to 3 ml were transferred into a series of 10 ml volumetric flasks and final volume was made up with buffer to give the concentration ranging from 5 µg/ ml to 30 µg /ml. the absorbance of these solutions was measured against a phosphate buffer pH 7.4 as a blank in UV/ Visible spectrophotometer at 252nm. Average of three determinations was taken.

Preformulations studies:

Preformulations testing is the first step in the rational development of dosage forms of a drug substance. It can be defined as " an investigation of physical and chemical properties of a drug substance alone and when combination with Excipients". The overall objective of preformulation testing is to generate information useful to the formulations in developing stable and bio available dosage forms that can be mass produced.The Preformulations scientist should consider the following before going through the formal program which includes:

- ✓ Available physico chemical data (including chemical structure and different salts avaliable).
- ✓ Anticipated dose.
- ✓ Supply situation and developing schedule.
- ✓ Availability of stability, assay.
- ✓ Nature of information the formulator should have or would like to have.

Hence, the following Preformulations studies were performed for the obtained sample of drug.

Formulation of Flupirtine tablets:

Step 1 : Maintained room conditions according to an aseptic area conditions.

Step 2 : Screening: Weighed quantity of Flupirtine was passed through sieve no 30#, talc and sodium starch glycolate passed through sieve 40#, and allow them to mix for about ten minutes.

Step 3: Lubrication : Finally the mixed compound was lubricated with magnesium stearate and aerosol for 10 minutes.

Step 4:Compression : lubricated materials were compressed into tablets using 8mm punch in a rotary tablet punching machine.

The Flupirtine tablets were prepared by direct compression method. The HPMC K100M,HPMC K4M is used as coating polymer which does not dissolves at 1.2pH and 6.8 pH but easily dissolved at pH 7.4 . Sodium starch glycolate is used as super disintergrating agent,magnesium stearate is used as glidant, and micro crystalline sellulose is used as diluents.

Table no.1: Formulation of Flupirtine tablets:

Composition(mg)	Formulation codes								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Flupirtine maleate	320	320	320	320	320	320	320	320	320
HPMC K 4M	80	40	60	40	80	40	60	80	60
HPMC K100M	60	100	80	60	80	80	60	100	100
Microcrystalline cellulose	55	55	55	95	35	75	75	15	35
Magnesium sterarate	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	520mg								

Post compression parameters:

a) Thickness:-

The thickness of tablets was determined with the help of veriner calipers.The thickness variation was allowed in the range of +5% of the size of the tablet.

b) Drug content in tablets :-

The tablet was triturated to form a fine powder and transferred to a100ml volumetric flask and dissolved in phosphate buffer pH 6.8 and was made up to the voume to get stock solution . 1ml of this stock solution was taken in a 100ml volumetric flask and diluted with phosphate buffer pH 6.8 and made up to the volume .the absorbance of this solution was measured at 252 mm using UV spectrophotometer. The drug content was estimated from the absorbance obtained.

c) Hardness:-

Hardness indicates at ability of the tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in Kg/cm^2. 5 tablets were randomly picked and hardness was determined.

d)Friability (Javadzadeh Y et.al,2005):-

Friability of the tablets was determined using Roche Friabilator. It is expressed in percentage (%) . Ten tablets were initially weighed ($W_{initial}$) and transferred into friabilator . The friabilator was operated at 25 rpm for 4 minutes or run upo to 100 revolutions .The tablets were weighed again (W_{final}).

The % friability was then calculated by –$F= W_{initial}-W_{final}\ x100/W_{initial}$

% Friability of the tablets less than 1% is considered as acceptance

e) Weight variation test :-

This is an process quality control test to ensure that the manufacturers control the variation in the weight of the compressed tablets . These tests are primarily based on the comparison of the weight of the individual tablets of a sampke of tablets with an upper and lower percentage limit of the observed sample average (x-mean)(koaml R et.at,2011)

f) Disintegration test :

For a drug to be absorbed from a solid dosage from after oral administration ,it must first be in solution ,and the first important step towards this condition is usually the break-up of the tablet; a process known as disintegration. The disintegration test is a measure of the time required under a given set of conditions for a group of tablets to disintegrate into particles which will pass through a 10 mesh screen..

g) In-vitro drug release studies:

Dissolution is the process by which a solid solute enters a solution . in the pharmaceutical industry, it may be defined as the amount of drug substance that goes into solution per unit under standardized conditions of liquid/solid interface , temperature and solvent composition . Dissolution is considered as one of the most important quality control test performed on pharmaceutical dosage forms and is now developing into a tool for predicting bioavailability.

Results and Discussion

Standardization Curve Of Flupirtine Maleate

Table no . 2: Standardization Curve Of Flupirtine Maleate:

S.no	Concentration (µg/ml)	Absorbance (250nm)
1	0	0
2	2	0.0681
3	4	0.1820
4	6	0.2550
5	8	0.3276
6	10	0.4230
7	12	0.5228
8	14	0.6295
9	16	0.7291

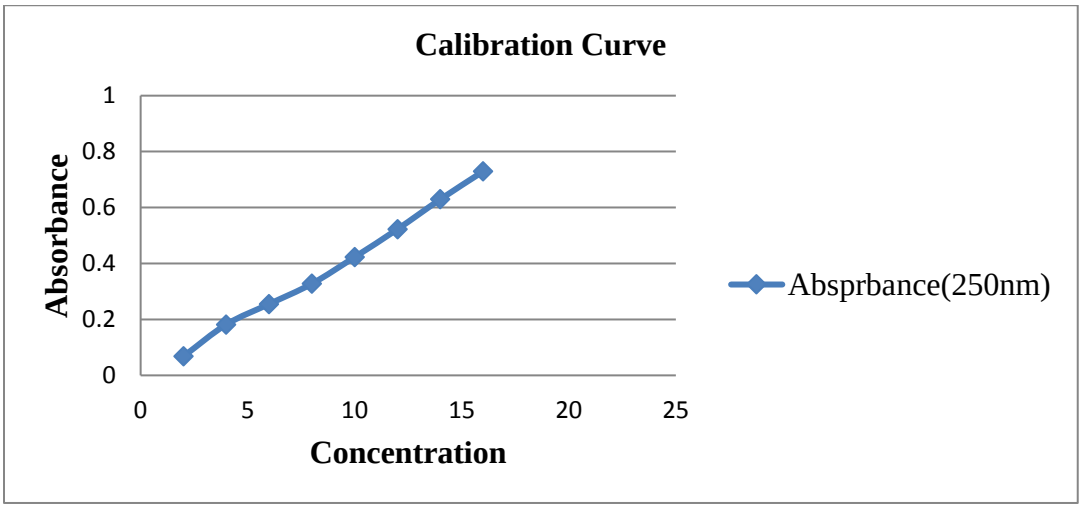

Fig.1 : Calibration curve of Flupirtine maleate in pH 6.8 buffer

FT- IR Spectroscopy(Fourier transform infrared spectroscopy)

A compatibility study focuses on a binary mixture of drug substance and some selected Excipients a fixed ratio with or without added moisture. The mixture stored at elevated temperatures as 40◦c 75%RH, 55◦c 60%RH in capped vials. The results of interaction between

the active drug and Excipients are determined as those IR spectra of mixture of Flupirtine maleate and HPMCK100M+HPMCK4M.

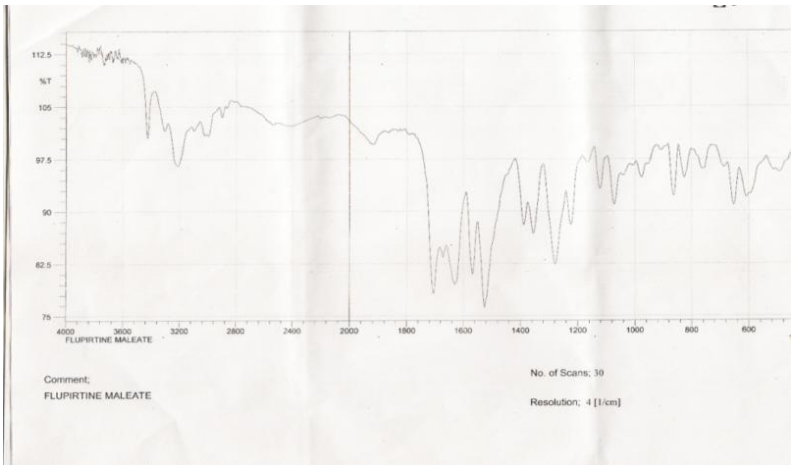

Fig.2 :FT- IR spectra of Drug Flupirtine Maleate

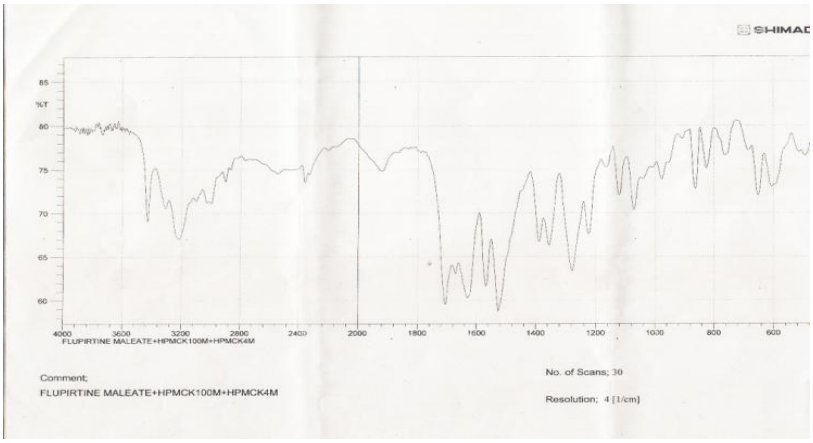

Fig.3 :FT-IR spectra of mixture of Flupirtine Maleate and HPMCK100M +HPMCK4M

Physiochemical Properties:

Characterization of Flupirtine tablets:

Pre compression parameters:

These test were performed as per procedure given in material and method part. The results are illustrated in following table.

Table No.3: physio chemical evaluation of Flupirtine powder

Pre Formulation	Angle of repose ± SD	Bulk density ± SD	Tapped density ± SD	Carr's index ± SD	Hausner's ratio ± SD
F1	23.79 ± 0.04	0.589± 0.020	0.727 ± 0.11	17.97 ± 0.50	1.216 ± 0.02
F2	23.77 ± 0.03	0.677 ± 0.03	0.851 ± 0.09	20.33 ± 0.88	1.255 ± 0.03
F3	26.83 ± 0.06	0.689 ± 0.03	0.869 ± 0.07	19.61 ± 0.62	1.27 ± 0.03
F4	25.16 ± 0.05	0.632 ± 0.04	0.743 ± 0.05	17.53 ± 0.53	1.16 ± 0.04
F5	25.61 ± 0.12	0.625 ± 0.02	0.726 ± 0.06	17.28 ± 0.80	1.163 ± 0.01
F6	21.27 ± 0.03	0.716 ± 0.04	0.833 ± 0.15	17.05 ± 0.32	1.161 ± 0.02
F7	24.11 ± 0.06	0.671 ± 0.12	0.848 ± 0.54	17.06 ± 0.43	1.243 ± 0.03
F8	24.14 ± 0.09	0.678 ± 0.05	0.784 ± 0.11	18.28 ± 0.06	1.172 ± 0.02
F9	21.03 ± 0.03	0.671 ± 0.03	0.826 ± 0.09	18.55 ± 0.93	1.221 ± 0.03

The Flupirtine tablets were prepared by direct compression method . Before compression the powder was evaluated for angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index .

The bulk densities of the powder were found to be in the range of 0.589 ± 0.020 to 0.716 ± 0.04 gm/ml, while the tapped densities were ranges between 0.726 ± 0.06 to 0.869 ± 0.07 gm/ml. the flow characteristics of the powder were assessed by determining their angle of repose and Carr's index . the low values of compressibility 17.05 ± 0.32 to 20.33 ± 0.88 signify good flowability.

The angle of repose of all formulation were less than 30^{O} (21.03 ± 0.03 to26.83 ± 0.06) , also indicated good flowability of the powder. This shows that the powder has smooth flow properties ensuring homogenous filling of the die cavity during the punching of tablets.

Post Compression parameters:

Physicochemical evaluation of uncoated tablet:

The Flupirtine tablets were prepared by direct compression method. The results of physicochemical evaluation of prepared tablets are shown in Table 5.5. the tablets were evaluated for hardness, diameter, thickness average weight of the tablet and drug content. The tablet were evaluated for their hardness, content uniformity, diameter, thickness, friability, disintegration and in vitro drug release. The hardness test is one of the control parameter during the manufacturing of tablets.

Generally the tablets prepared with low compression force dissolves faster than that with high compression force. The recommended hardness value for tablet is 4 to 8 kg/cm. the average hardness of the tablets was found to be in range of 6.7 ± 0.19 to 7.4 ± 0.24 kg/cm2 .

Table No.4: evaluation of sustained release Bilayer tablet of Flupirtine maleate

Formulation	Hardness (kg/cm2)	Wt.variation(mg)	Thickness (mm)	% Fribility	Invitro disintegration time (sec)
F1	7.0±0.23	721.1± 3.56	7.38 ± 0.21	0.73 ± 0.10	98.87%
F2	7.1 ± 0.16	721.7 ± 2.42	7.46 ± 0.18	0.74 ± 0.16	99.74%
F3	6.8 ± 0.41	718.9 ± 1.97	7.52 ± 0.22	0.75 ± 0.32	98.6%
F4	7.2 ± 0.31	720.6 ± 3.11	7.34 ± 0.16	0.72 ± 0.24	98.16%
F5	6.7 ± 0.19	720.7 ± 3.16	7.62 ± 0.14	0.81 ± 0.24	98.87%
F6	6.92± 0.20	722.7 ± 2.16	7.48 ± 0.21	0.73 ± 0.19	99.74%
F7	7.16± 0.37	720.8 ± 2.31	7.38 ± 0.25	0.72 ± 0.41	99.65%
F8	7.4 ± 0.24	720.7± 4.076	7.51 ± 0.240	0.74± .063	96.62%
F9	7.3 ± 0.21	718.6 ± 2.12	7.22 ± 0.14	0.72 ± 0.29	99.36%

The average weight variation of the tablets was found within the limits of 718.6 ± 2.12 to 722.7 ± 2.16. friability value of tablets should be in range of 0.5 to 1% limits, which is the usual friability range of tablets range of 0.72 ± 0.24 to 0.81 ± 0.24.

The content uniformity of drug Flupirtine present in the tablets formulation ranged from the thickness of the tablet was found to be 7.22 ± 0.14 to 7.62 ± 0.14. It was found that the physicochemical parameters of the prepared tablets comply with standards.

Disintegration time:

The disintegration time is equivalent to 10mg of Flupirtine maleate was accurately weighed from powdered bilayred tablets and it was dissolved in distilled water to form a clear solution.

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.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.

Table no.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	Marketed product
1	0	0	0	0	0	0	0	0	0	0	**0**
2	1	31.62	23.47	26.12	29.25	29.24	22.48	28.19	26.45	30.75	**25.80**
3	2	36.42	34.52	34.87	33.42	34.28	31.67	35.95	33.36	38.54	**32.40**
4	3	41.47	41.65	46.45	38.24	42.66	42.45	45.24	41.16	47.62	**38.25**
5	4	48.98	48.45	53.94	46.14	46.87	49.67	54.09	44.86	52.81	**42.54**
6	5	53.65	55.31	59.40	52.78	49.77	58.33	60.27	48.71	58.38	**48.70**
7	6	59.52	58.86	65.65	60.50	54.11	59.27	66.87	52.25	63.17	**51.25**
8	7	64.58	62.59	68.99	69.25	57.31	64.14	68.23	56.86	67.40	**55.80**
9	8	69.29	69.67	72.28	78.86	62.35	68.27	74.49	61.63	71.37	**58.62**
10	9	73.79	74.51	75.95	85.10	68.41	79.55	76.98	64.95	78.23	**62.50**
11	10	79.29	82.76	80.87	92.174	75.58	91.39	82.26	70.15	81.51	**68.30**
12	11	86.72	89.16	86.73	95.38	81.39	92.27	87.85	75.36	87.49	**72.86**
13	12	91.42	93.56	91.49	98.16	89.43	96.50	92.95	80.92	95.35	**74.12**
14	14	95.31	97.95	95.01	-	94.83	99.74	99.65	83.6	96.30	**81.78**
15	16	98.87	99.74	98.6	-	98.87	-	-	89.30	99.36	90.82
16	18	-	-	-	-	-	-	-	96.62	-	96.59

For formulations of F1 to F9:

The results of the In-vivo release studies were tabulated and the release profile is plotted in the chart.

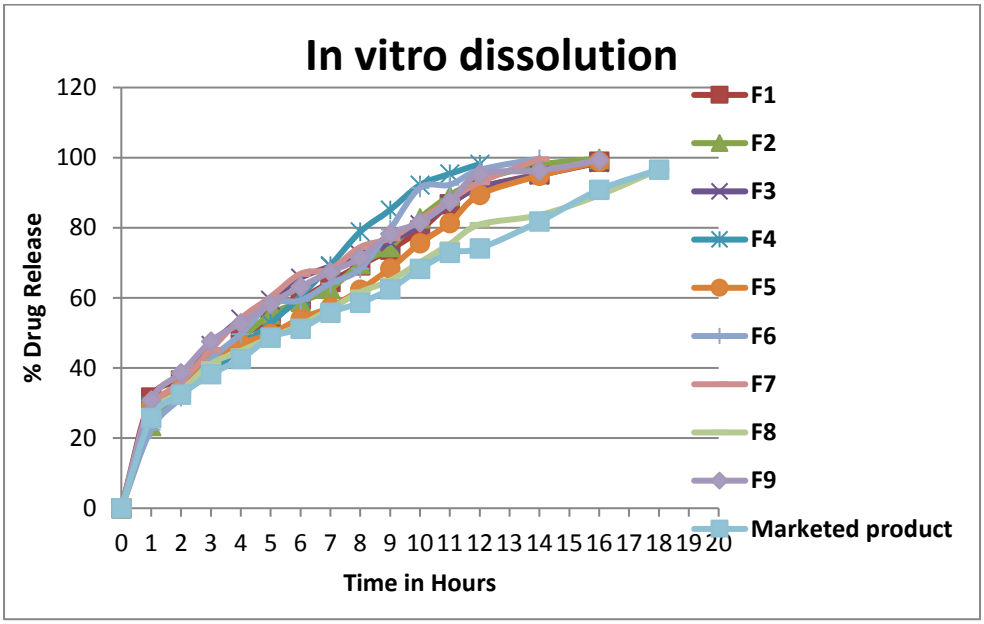

Fig 4: Time vs % drug release for formulations F1 to F9 with comparative of marketed product

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. The percentage drug release shows formulations (F1-F9) in the range of 99.74 % to 96.62% for F2 and F8.

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 No.6 In vitro drug release data of Flupirtine maleate from optimized formulation F8 and marketed product:

Time in hrs	0	1	4	8	12	18
% drug release in F8	0	26.45	44.86	61.63	80.92	96.62
% drug release in marketed product	0	25.80	42.54	58.62	74.12	96.59

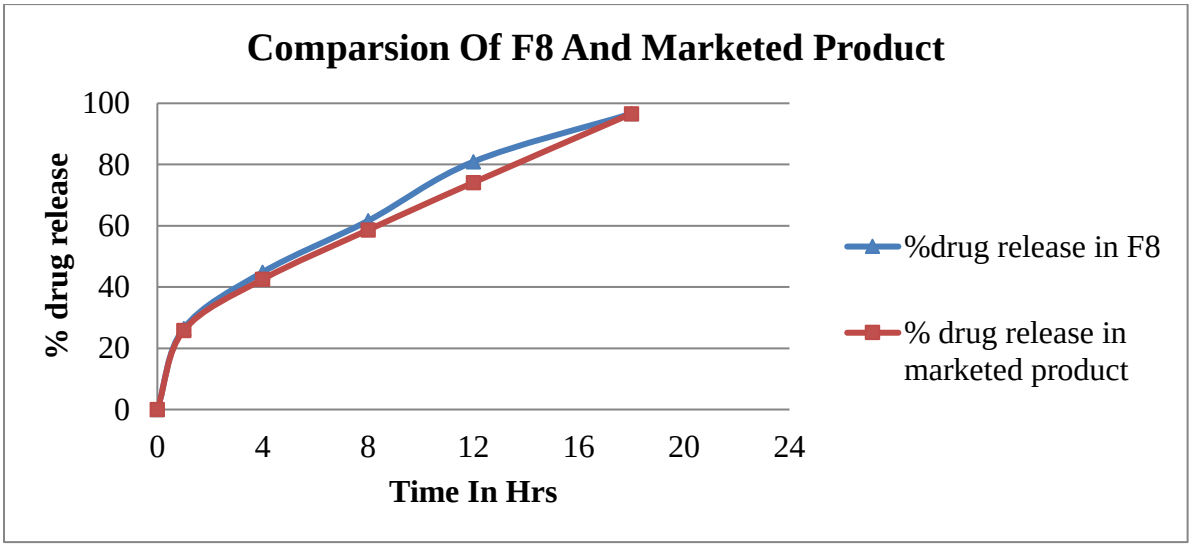

Fig .5: Time vs % drug release for formulations F8 and marketed product in comparison

Kinetics of drug release:

In vitro dissolution has been recognized as an important release element in drug development. Under the certain conditions it can be used as a surrogate for the assessment of bioequivalence.

The quantitative interpretation of the values obtained in the dissolution assay is facilitated curve in function of some parameters related with the pharmaceutical dosage forms. In some

cases, that equation can be deduced by a theoretical analysis of the process, as a example in zero order kinetics. In most cases, with tablets, capsules, coated forms or prolonged model dependent (curve fitting), statistical analysis and model independent methods can be used.

The various release kinetic equation in which the experimental data can be fitted and drug release rate can be predicted as a function of some variable are mentioned below. The suitability of equation is judged on the basis of best fit to the equation using statistical indicators like R2 value.

A. ZERO ORDER % DRUG RELEASE KINETICS:

The equation describing the kinetics is depicted in equation

$$\mathbf{Qt = Qo + Kot}$$

Where,

Qt is the initial amount of drug dissolved at time t,

Qo is the initial amount of drug in the solution, most of the times it is equal to zero,

Kot is the zero order release rate constant.

Dosage forms following this profile, release same amount of drug per unit time, and it is the ideal method of release for a sustained release product.

B. FIRST ORDER %DRUG RELEASE KINETICS:

The applications of this model of drug dissolution studies were first proposed by Gibaldi and Feldman in 1967.

$$\mathbf{Qt = Qo^{e\text{-}kt}}$$

(or)

In (Qt/Qo) = K1t (or) In Qt = In QoK1t

(or)

Log Qt = log Qo + (k1t/2.303)

Where,

Qt is the initial amount of drug dissolved at time t,

Qo is the initial amount of drug in the solution,

K1 is the first order release rate constant.

In this way a graphic of the decimal log of the release amount of drug vs time will be linear. The pharmaceutical dosage forms following this dissolution profile, such as those containing water soluble drugs in the porous matrics would release the drug in a way that is proportional to amount of drug remaining in its interior.

Table no. 7: R2 value of drug release kinetics models of optimized formula F8

S.no	Model	R2 value
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 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.

The erosion model was applied to *in vitro* release data, the linearity was observed with r2value and also Hixon-Crowell cube root model showed high r2 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 in vitro dissolution 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.

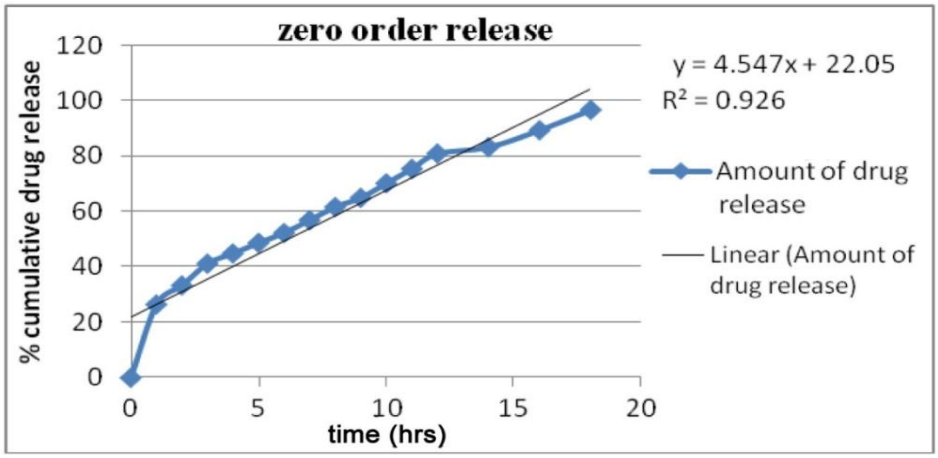

Fig 6: zero order drug release model of the optimized formulation

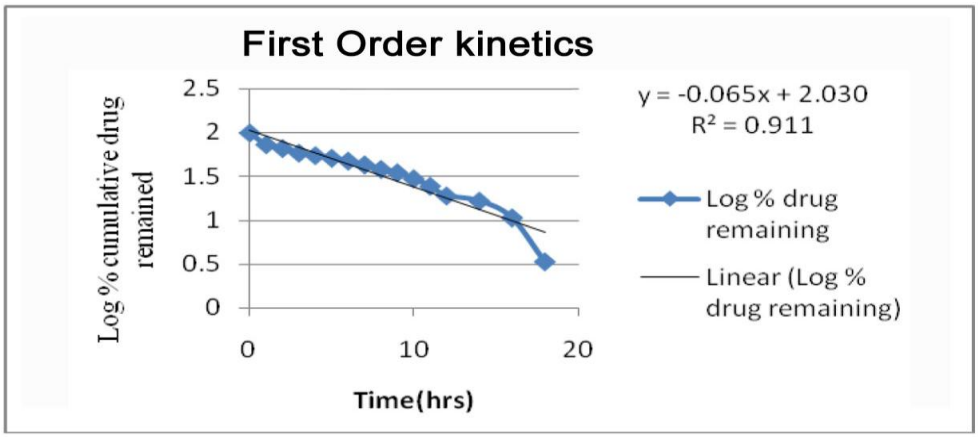

Fig. 7: First order drug release model of the optimized formulation F8

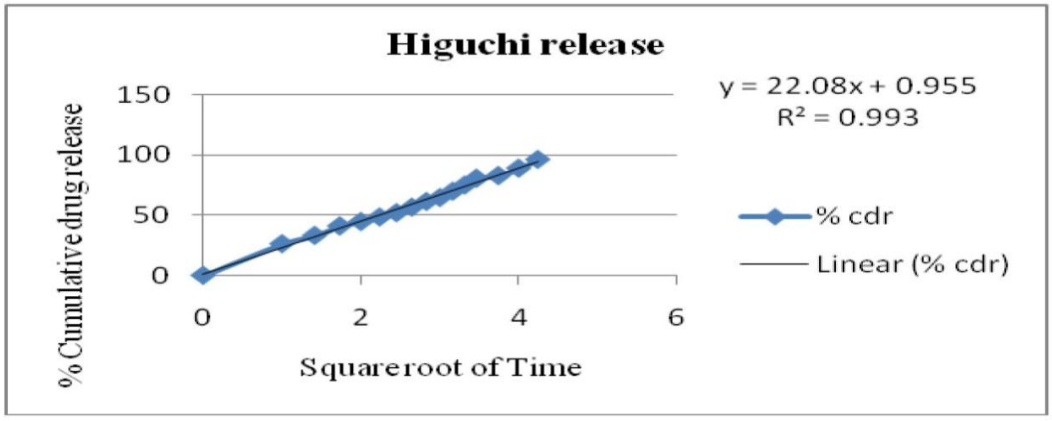

Fig. 8: Higuchi drug release model of the optimized formulationF9

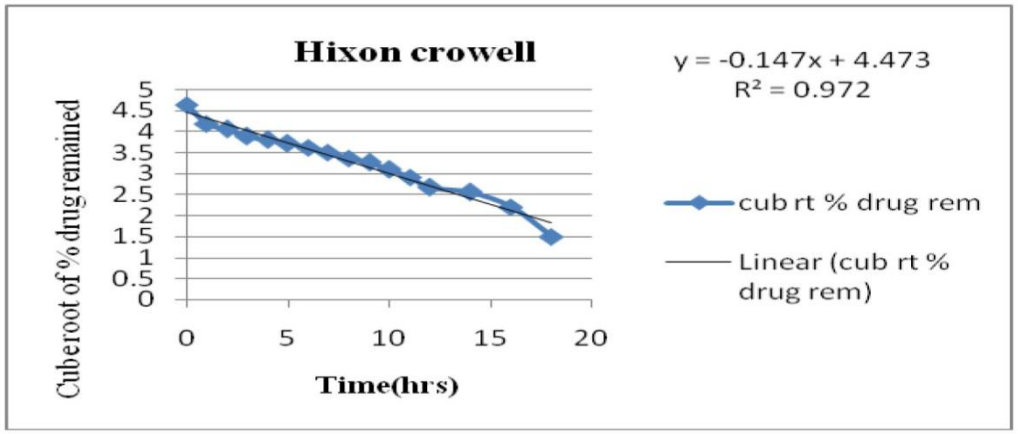

Fig. 9:.Hixon-Crowell model of the optimized formulationF9

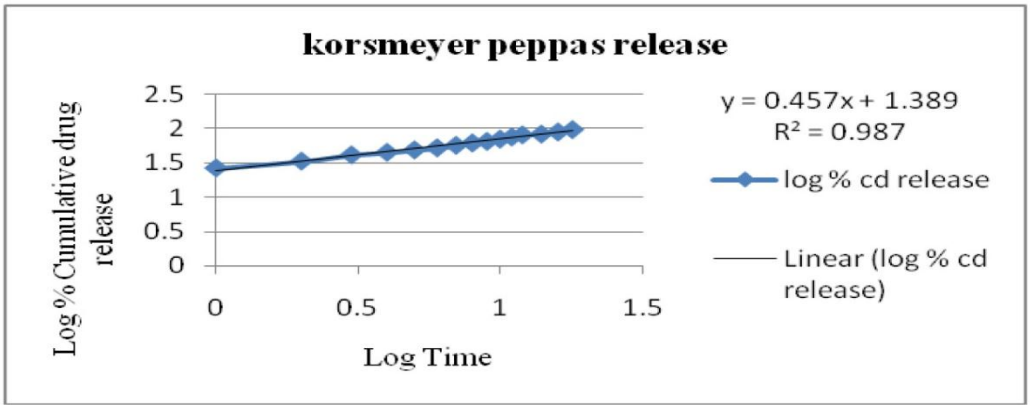

Fig. 10: Korsmeyer peppas drug release model of the optimized formulationF9

Table No.8 : Mathematical modeling and drug release kinetics of optimized formulation F8 and marketed product

Formulation	Drug release kinetics (R2)				Release exponential(n)
	Zero- order	First –order	Huguchi	Korsmeyer	
F8	0.926	0.911	0.993	0.972	0.987
Marketed product	0.934	0.912	0.993	0.974	0.990

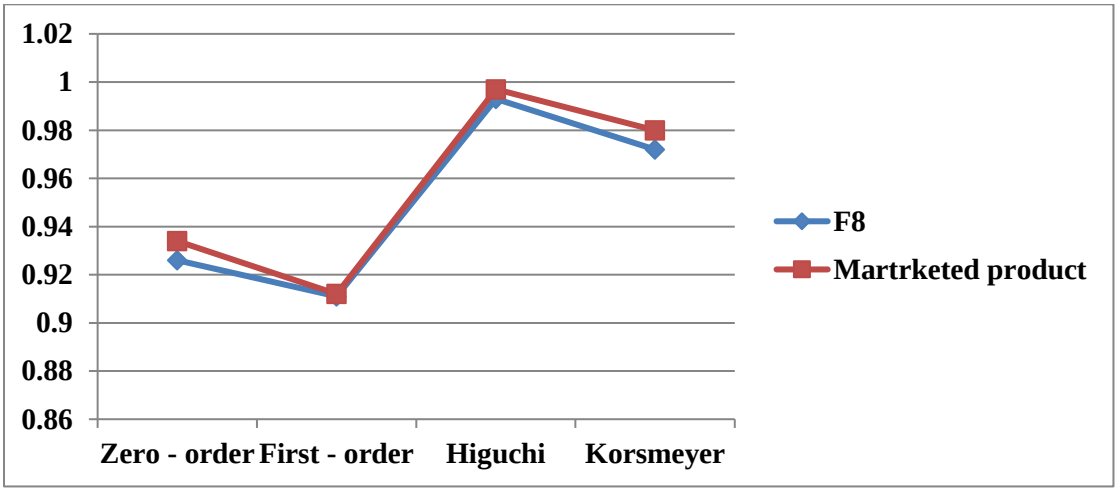

Fig. 11: Mathematical modeling and drug release kinetics of optimized formulation F8 and marketed product

Results of Stability Studies:

Table No,9 Results of Flupirtine Maleate Stability Studies:

Parameters tested	Storage conditions			
	Initial	40◦c ± 2◦c / 75% ± 5% RH		
		1 st month	2nd month	3rd month
Description	White crystalline powder	Non change	No change	No change
Weight(mg) variation	720	720	720	719
Thickness (mm)	7.51	7.51	7.51	7.49
Hardness (kp)	7.4	7.4	7.4	7.1
Friability (%)	0.74	0.74	0.74	0.73

Discussion

The drug release data obtained were extraplotted by zero order, higuchi, first order, korsemeyer peppa's to know the mechanism of drug release from the formulations. The release rate kinetic data for all the formulations was shown in table No 16. The release kinetics shows that the release of drug followed first order release in all formulations as the drug fitted in first order kinetics, indicating that the rate of drug release is concentration dependent.

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 F8 by adopting biphasic drug release pattern in a single dosage could improve patient compliance and give better pain management.

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