Advances in Bioresearch
Adv. Biores., Vol 12 (3) May 2021: 49-58
©2021 Society of Education, India
Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.12.3.4958

Advances in Bioresearch

ORIGINAL ARTICLE

Formulation and Evaluation of Sustained Release Matrix Tablets of Oseltamivir Phosphate

M.P. Kusuma*,Asma Ul Husna And M.Sumakanth
RBVRR Women's College of Pharmacy; Barkatpura, Hyderabad
(Affiliated To Osmania University)

ABSTRACT
Oseltamivir (marketed as the product Tamiflu), is an antiviral neuraminidase. activity It hinders the activity of the viral neuraminidase enzyme. The aim of the present study is to developed formulation and evaluation of sustained release matrix tablets of Oseltamivir phosphate. Total 13 formulations were prepared by wet granulation method by using hydrophilic polymers (HPMCK 15M HPMC E50), and hydrophobic polymers such as (Eudragit RL 100, Ethyl cellulose), in the ratios (1:0.25,1:0.5,1:1) with other excipients like PVPk30, Iso-propyl alcohol, MCC, Magnesium stearate and Talc. Pre-formulation parameters like angle of repose. tapped density, bulk density, carr's index, hausner's ratio was found to be within the limits and the prepared tablets were evaluated for hardness, friability, weight variation, swelling index, drug content, in-vitro drug release for 10 hr. All the formulations have showed acceptable Pharmacopeial standards. Between the two hydrophilic polymers, F1 formulation composed of the drug and HPMCK15 in the ratio of 1:0.25 was observed to have better in vitro drug release after 10hr time compared to F4 and by comparing the two hydrophobic polymers, F7 formulation composed of the drug and Eudragit RL 100 in the ratio of 1:0.25 was having was having good dissolution profile when compared to F10.The combined effect of hydrophilic and hydrophobic polymer in dissolution profile of the drug was checked and it was found that F13 formulation was showing uniform drug release for extended period of time as compared to other formulations. So, F13 formulation in the ratio of (1:1) was selected as the best formulation. Our research concludes the kinetics of drug release followed zero order kinetics and the drug release mechanism is erosion and diffusion. The optimized formulation was found to be stable after 5 months.
Key words: *Oseltamivir phosphate, sustained, HPMC K15m, Eudragit RL 100.*

Received 11.02.2021 Revised 12.04.2021 Accepted 03.05.2021

How to cite this article:
M.P. Kusuma,, Asma Ul Husna And M.Sumakanth. Formulation and Evaluation of Sustained Release Matrix Tablets of Oseltamivir Phosphate. Adv. Biores. Vol 12 [3] May 2021. 49-58

INTRODUCTION

Sustained release, sustained action, prolonged action-controlled release, extended release, depot release these are the varied terms want to identify drug delivery systems that are designed to realize a protracted therapeutic effect by continuously releasing medication over an extended period of your time after administration of one dose of drug [1-5]. The goal in developing sustained release delivery systems is to scale back frequency of dosing or to extend effectiveness of the drug by reducing dose required or providing prolonged action in dosage form drug delivery [6-11]. These delivery systems have difference in benefits over traditional systems like improved efficiency, reduced toxicity, and improved patient convenience. the most goal of sustained drug delivery systems is to enhance the effectiveness of drug therapy. Sustained release tablets are generally taken once or twice each day during a course of treatment whereas in conventional dosage forms there's got to take 3-4 times dosage during a day to realize an equivalent therapeutic action. The key role behind administering one dose of a drug of sustained release dosage forms is that it is often released over an extended period of your time to take care of uniform concentration of a drug during a blood this might cause better patient compliance and supply enhanced clinical output of the drug [12-16].

Oseltamivir phosphate is an anti-viral drug used for the treatment of infections with the influenza virus. This drug is water soluble with good oral availability [17]. At present, there is no sustained

release dosage form available for oseltamivir phosphate in market. Tablets are unit solid dosage forms and are of widely accepted because of its convenience of self-administration, cost-effective manufacturing and better patient compliance [18-22].
The objective of the present investigation is to formulate and evaluate of oseltamivir phosphate sustained -release matrix tablets by using hydrophilic and hydrophobic polymers.

CALCULATION OF SUSTAINED-RELEASE DOSE AND THEORETICAL RELEASE

To maintain the therapeutic level &sustainability for a given period of time for the dosage form generally consist of two parts. [17]
The total dose of Oseltamivir phosphate for twice-daily SR formulation was calculated by Robinson Eriksen equation using available pharmacokinetic data. The kinetics drug release for zero-order drug release rate constant (k_0) was calculated by using following equation.
$k_0 = D_I \times k_e$
where DI is the initial dose (i.e., conventional dose = 30 mg) and
ke is first order rate constant for overall elimination.; $k_e = 0.693 / t_{1/2}$;
where $t_{1/2}$ = Biological half-life of Oseltamivir phosphate = 3hrs.
Therefore $k_e = 0.693 / 3 = 0.231$ mg/h.
Availability rate $R = k_e \times D_I = 0.231 \times 30 = 6.93$mg/h.
Loading dose = $D_L = D_I - R^* t_{max}$
where t_{max} = 1.5 h Therefore $D_L = 30-(6.93 \times 1.5) = 19.6$ mg.
Maintenance dose = $D_M = R \times H$
Where, H = Number of hours for which sustained action is desired after initial release.
Therefore $D_M = 6.93 \times 12 = 83.16$ mg.
Total dose required D_T
$D_T = D_L + D_M = 19.6+83.16 = 102.76$ mg
103mg
Hence an oral sustained release formulation of Oseltamivir phosphate should contain a total dose of 103 mg.

MATERIAL AND METHODS

Oseltamivir Phosphate, Hpmc K15m, Hpmc E50, Eudragit Rl 100, Ethyl Cellulose, Pvp K30, Iso-Propyl Alcohol, Mcc, Magnesium Stearate, Talc.

ANALYTICAL DEVELOPMENT

Development of Calibration curve for Oseltamivir phosphate

Standard curve of Oseltamivir phosphate was prepared by dissolving known amount of drug in water. The respective absorbance was read using phosphate buffer as blank at λmax 221nm, by using UV-Visible spectrophotometer. The standard graph was found to be linear with R^2 value of 0.999 in the concentration range of 2-10 µg/mlas shown in the fig 1.

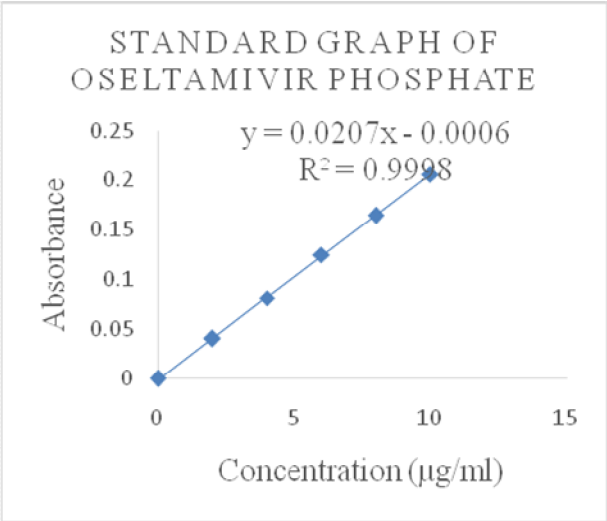


Fig1: Standard graph of Oseltamivir Phosphate

PREPARATION OF OSELTAMIVIR PHOSPHATE SUSTAINED RELEASE TABLETS BY WET GRANULATION METHOD.

Matrix Tablets –Different formulations of each containing 103mg of Oseltamivir phosphate, were prepared by wet granulation method. [21]

Wet granulation: Drug and the excipients were strained into mortar and mixed well to obtain uniformity of premixed blend. This Powdered blend was wet granulated with 5% w/v solution of PVP K-30 in a mortar. The wet mass was passed through sieve no.18. The wet granules were dried at 40°C ± 5°C for 5 min in a hot-air oven and the dried granules were sieved through sieve no 22. These granules were blended with lubrication mixture (magnesium stearate and talc) and compressed using 16 station rotary tableting machine, equipped with flat-faced, round punches of 8-mm diameter. The formulations prepared, by using release retardants polymers as hydroxypropyl methylcellulose HPMC K15M HPMC E 50,polyacrylate polymer used is Eudragit RL 100, Ethyl cellulose and microcrystalline cellulose (MCC) was used as diluent. Magnesium stearate (MS) and talc was used as lubricant and glidant. 5% w/v solution of polyvinylpyrrolidone (PVP-K30) in isopropyl alcohol (IPA) was used as binder. A composition of formulation was given in the following Table 1&2.

Table 1: Formulation of Oseltamivir SR tablets by wet granulation method

INGREDIENTS	F1mg	F2mg	F3 mg	F4 mg	F5 mg	F6 mg	F7 mg
OSELTAMIVIR PHOSPHATE	103	103	103	103	103	103	103
HPMC K15 M	25.69 (1:0.25)	51.38 (1:0.5)	103 (1:1)				-
HPMC E50 M	-	-	-	25.69 (1:0.25)	51.38 (1:0.5)	103 (1:1)	
EUDRAGIT RL 100	-	-	-	-	-	-	25.69 (1:0.25)
ETHYL CELLULOSE	-	-	-	-	-	-	-
PVP K 30	5	5	5	5	5	5	5
ISO -PROPRYL ALCOHOL	Qs	Qs	qs	qs	Qs	Qs	Qs
MCC	135	161	83	135	161	83	135
MAGENESIUM STEARATE	3	3	3	3	3	3	3
TALC	3	3	3	3	3	3	3
TOTAL WEIGHT	300	300	300	300	300	300	300

103 mg of Oseltamivir phosphate is ~ to 78.40mg of Oseltamivir

Table no 2: Formulation of Oseltamivir SR tablets by wet granulation method

INGREDIENTS	F8 mg	F9 mg	F10mg	F11mg	F12mg	F 13mg
OSELTAMIVIR PHOSPHATE	103	103	103	103	103	103
HPMC K15 M	-	-	-	-	-	25.69 (1:1)
HPMC E50 M	-	-	-	-	-	-
EUDRAGIT RL 100	51.38 (1:0.5)	103 (1:1)	-	-	-	25.69 (1:1)
ETHYL CELLULOSE	-	-	25.69 (1:0.25)	51.38 (1:0.5)	103 (1:1)	-
PVP K 30	5	5	5	5	5	5
ISO-PROPRYL ALCOHOL	Qs	qs	qs	Qs	Qs	qs
MCC	161	83	135	161	83	135
MAGENESIUM STEARATE	3	3	3	3	3	3
TALC	3	3	3	3	3	3
TOTAL WEIGHT	300	300	300	300	300	300

103 mg of Oseltamivir phosphate is ~ to 78.40mg of Oseltamivir

PRE-COMPRESSION PARAMETERS OF SUSTAINED RELEASE TABLET OSELTAMIVIR PHOSPHATE

Pre compression parameters of all formulations blend were conducted such as angle of repose, bulk density, tapped density, compressibility index and hausners ratio. The two most important attributes for the wet granulation formula are having good flow and good compressibility property.

Table No 3: Pre -Compression Parameters of Powder Blend of Oseltamivir Phosphate SR tablets

Formulation Code	Angle of repose (°)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's Index (%)	Hausner's Ratio
F1	28.21± 0.041	0.515±0.015	0.522±0.008	13.15±1.04	1.10±0.07
F2	31.3± 0.014	0.477±0.004	0.476±0.012	16.23±0.23	1.21±0.11
F3	28.05± 0.013	0.505±0.005	0.527±0.015	14.26±0.65	1.15±0.31
F4	26.33± 0.024	0.522±0.023	0.519±0.022	12.36±0.26	1.09±0.23
F5	25.37± 0.023	0.466±0.025	0.476±0.012	16.22±0.23	1.21±0.11
F6	24.13± 0.022	0.505±0.005	0.531±0.005	14.26±0.65	1.15±0.31
F7	27.61± 0.030	0.469±0.026	0.619±0.022	12.36±0.26	1.09±0.23
F8	19.09± 0.020	0.471±0.017	0.469±0.012	16.25±0.23	1.21±0.11
F9	16.73± 0.014	0.471±0.013	0.467±0.003	16.26±0.23	1.21±0.11
F10	24.76± 0.010	0.501±0.005	0.612±0.022	12.12±1.20	1.14±0.01
F11	26.55± 0.013	0.491±0.009	0.513±0.009	11.27±1.34	1.14±0.03
F12	29.09± 0.020	0.461±0.011	0.521±0.011	11.20±1.29	1.12±0.02
F13	27.46± 0.011	0.505±0.018	0.513±0.005	13.36±0.26	1.10±0.08

Values expressed in X± SD (mean± standard deviation)

RESULTS

PRE-COMPRESSION PARAMETERS

Drug Properties: The drug flow character is observed as excellent, good, fair based on the compressibility index and Hausner's ratio according to the limits mentioned in table 4in which the powder flow property of drug can be increased by the addition of excipients.

Angle of repose: The Angle of repose of all the formulations [F1-F13] developed in the formulation's development phase was found to be excellent to fair i.e., 24.76±0.010 to31.11±0.014 shown in the table 3.

Bulk Density (BD): The powder blends of formulations F1-F13 have the bulk density ranged between 00.461±0.011 to 0.522±0.023 shown in the table 3.

Tapped Density (TD): The powder blends of formulations F1-F13 have the tapped density ranged between 0.467±0.003to 0.619±0.022shown in the table 3.

Carr's index: Carr's Index or Compressibility Index (%) of all the formulations [F1-F13] developed in the formulation's development phase was found to be excellent to fair i.e., 11.20±1.29 to 16.23±0.23 shown in the table 3.

Hausner's ratio: The Hausner's ratio of all the formulations [F1-F13] developed in the formulation's development phase was found to be excellent to fair i.e., 1.09±0.23 to 1.21±0.11shown in the table 3.

EVALUATION OF POST -COMPRESSION OF SUSTAINED RELEASE TABLET OSELTAMIVIR PHOSPHATE

Table no 4 Post -Compression Parameters of Oseltamivir phosphate SR Tablets

Formulation code	%Weight Variation	Hardness kg/cm² (n=3)	Friability (n=3) (%)	Thickness (mm)	Swelling Index (%)	Drug Content
F1	296±0.02	5.6±0.408	0.11±0.06	6.12	39.31	97.25
F2	293±0.05	5.2±0.05	0.18±0.01	6.10	45.42	96.12
F3	295±0.04	5.3±0.05	0.13±0.02	6.11	42.51	97.43
F4	293±0.07	5.2±0.08	0.18±0.01	6.11	41.73	96.05
F5	294±0.05	5.4±0.04	0.18±0.01	6.14	43.51	95.12
F6	296±0.04	4.8±0.05	0.16±0.02	6.12	47.53	95.31
F7	293±0.06	4.6±0.04	0.16±0.03	6.13	32.45	97.48
F8	292±0.08	5.4±0.04	0.16±0.02	6.14	43.41	95.14
F9	294±0.07	5.8±0.05	0.15±0.03	6.11	42.71	96.23
F10	293±0.05	5.7±0.6	0.16±0.05	6.11	46.31	95.37
F11	292±0.07	5.6±0.5	0.11±0.06	6.12	43.61	96.45
F12	295±0.04	5.3±0.6	0.13±0.07	6.10	42.14	95.24
F13	298±0.02	5.5 ±0.3	0.11±0.6	6.11	47.67	99.81

Values expressed in X± SD (mean± standard deviation)

Weight variation: weight variation test revealed that all the formulations [F1-F13] developed in the formulation's development phase was within the 292 to 298 & there is no much variation between the formulation pharmacopeial limits shown in the table 4.

Hardness: Hardness test revealed that all the formulations [F1-F13] developed in the formulation's development phase was in the range of 4.6±0.04 to 5.8±0.05kg/cm^2 shown in the table 4.

Friability: None of the formulated tablets had a percentage friability of more than 1% shown in the table 6and hence all batches passed the friability test . hence it was observed that mechanical strength of the formulated tablets showed no much difference for all the tablets containing different drug polymer ratios.

Thickness: Thickness test revealed that all the formulations [F1-F13] developed in the formulation's development phase was in the range of 6.10 to 6.14 mm shown in the table 4. All the formulations showed uniform thickness.

Swelling index: -Swelling index revealed that all the formulations [F1-F13] developed in the formulation's development phase was in the range of 39.31to 47.67% shown in the table 4.

Drug content: -drug content revealed that all the formulations [F1-F13] developed in the formulation's development phase was in the range of 96.05 to 99.81shown in the table 4.

All the formulated batches tablets had their drug content within the stipulated range. All the formulations tablet shows good acceptable pharmaco technical properties and complied with the USP specifications for weight variation, drug content, hardness, and friability.

***IN VITRO* DRUG -RELEASE OF OSELTAMIVIR PHOSPHATE SR TABLETS**

All the formulations of Oseltamivir phosphate were subjected to ***in-vitro*** release studies these studies were carried out using dissolution apparatus. The dissolution bath consisted of volume of 900 ml of standard buffer pH 1.2 for the first 2 h, followed by pH 6.8 for remaining period of time. The release of the drug from sustained release tablet of the various formulations varied according to the ratio and degree of the different polymer. The invitro drug release for the formulations F1-F6 formulated with hydrophilic polymer HPME K15 F1was found to have good drug release (89.63%) at 10hrs of time then compare to HPMC E50 ranges F4 (87.11%) drug release at 8hrs of time. The *in vitro* drug release for the formulations (F7-F12) formulated using hydrophobic polymers in this category F7 formulated exhibited a good drug release containing Eudragit (84.38%) at 10hrs of time. compare to Ethyl cellulose F10 exhibited drug release (86.17%) at 8hrs of time. In order to study the combined effect of polymers on the drug release profile, F13 formulation composed of HPMC K15 and Eudragit in the ratio of (1:1) was investigated, and it was observed that this F13 formulated extended the release of the drug till 10 hrs producing a drug concentration of (94.78%).Thus, it can be stated that F13 formulation can be an optimized formulation. The results are tabulated (Table no -5)

Table No5 *In Vitro* Drug -Release of Oseltamivir Phosphate Sr Tablets

Time in hrs	% Drug release (X±S.D)					
	F1	**F2**	**F3**	**F4**	**F5**	**F6**
0	0	0	0	0	0	0
1	12.13±0.041	16.35±0.05	13.71±0.36	15.51±0.07	12.41±0.06	13.71±0.11
2	23.21±0.051	26.12±0.04	25.31±0.01	24.02±0.11	25.41±0.05	26.41±0.07
3	29.83±0.02	32.21±0.09	34.02±0.09	31.65±0.28	33.43±0.14	33.61±0.07
4	38.12±0.04	45.31±0.14	45.61±0.31	43.31±0.08	47.61±0.12	44.71±0.07
5	43.21±1.12	53.13±0.11	54.14±0.16	53.05±0.03	56.74±0.06	53.63±0.10
6	55.14±0.07	65.61±0.8	66.04±0.02	68.51±0.06	69.01±0.01	65.06±0.07
7	69.15±0.04	75.51±0.24	79.51±0.08	79.61±0.06	77.09±0.07	79.76±0.07
8	76.11±0.02	83.841±0.45	89.45±1.36	87.11±0.04	88.62±0.07	86.36±0.04
9	83.41±0.01	88.68±0.35	-	-	-	-
10	89.63±0.02	-	-	-	-	-

Values expressed in n ± SD (mean± standard deviation)

Table no 6 – *In Vitro* Drug Release of Oseltamivir Phosphate Sr Tablet

Time in hrs	% Drug release (X±S.D)					
	F7	**F8**	**F9**	**F10**	**F11**	**F12**
0	0	0	0	0	0	0
1	12.41±0.07	14.71±0.07	13.71±0.05	11.23±0.043	16.15±0.05	17.14±0.36
2	25.13±0.01	28.42±0.09	27.72±0.13	25.29±0.055	29.22±0.04	29.83±0.01
3	32.41±0.07	33.61±0.04	31.42±0.12	32.30±0.02	31.21±0.09	32.12±0.09
4	41.71±0.07	41.51±0.04	43.27±0.01	45.21±0.04	45.13±0.14	47.06±0.02
5	50.61±0.06	45.12±0.02	47.41±0.04	53.12±1.12	50.03±0.11	51.24±0.16
6	56.41±0.05	55.64±0.02	54.48±0.05	67.41±0.07	63.11±0.8	64.14±0.02
7	63.84±0.07	68.65±0.02	60.15±0.04	74.51±0.04	79.41±0.24	73.15±0.08
8	72.75±0.05	78.61±0.06	76.06±0.02	86.17±0.02	85.61±0.45	84.25±0.03
9	79.51±0.03	85.51±0.01	83.52±0.03	-	-	-
10	84.48±0.02	-	-	-	-	-

Values expressed in n ± SD (mean± standard deviation)

Table No 7 In Vitro Drug Release of Oseltamivir Phosphate Sr Tablet

Time in hrs	F 13 % DR	Time in mins (marketed formulation) IR	F14 % drug release marketed formulation
0	0	5	23.41
1	15.46±0.36	10	30.23
2	27.83±0.01	15	49.26
3	33.22±0.09	30	89.41
4	43.36±0.02	45	100
5	52.24±0.16		
6	67.45±0.02		
7	75.10±0.08		
8	83.45±0.03		
9	90.13±0.02		
10	94.78±0.03		

Values expressed in n ± SD (mean± standard deviation)

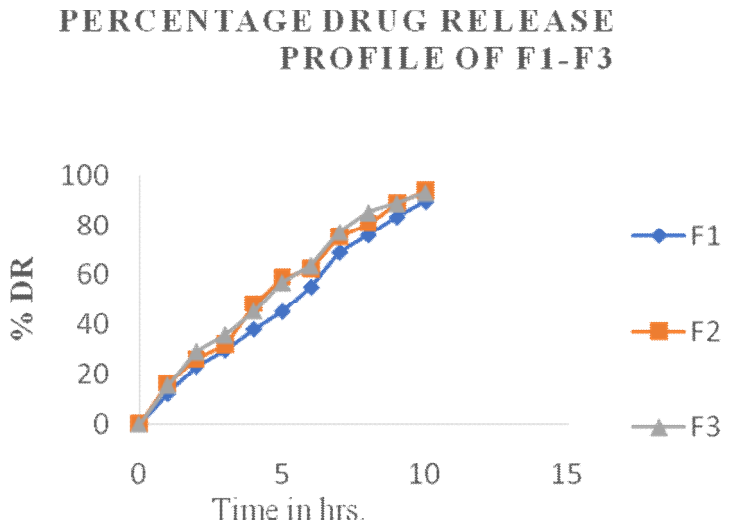


Fig.no 2 Percentage Drug Release Profile FormulationF1- F3 by using HPMC K 15M

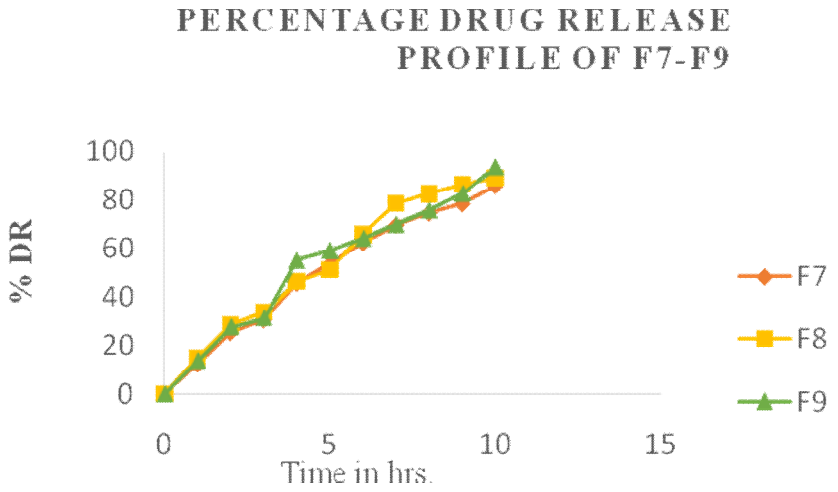


Fig.no3Percentage Drug Release Profile Formulation F7- F9 by using Eudragit RL100

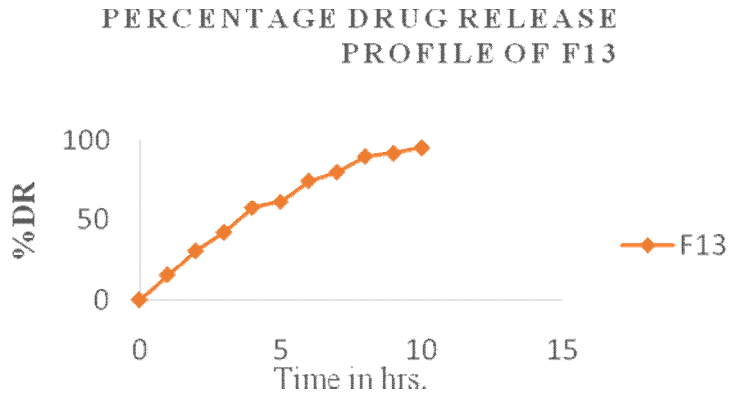
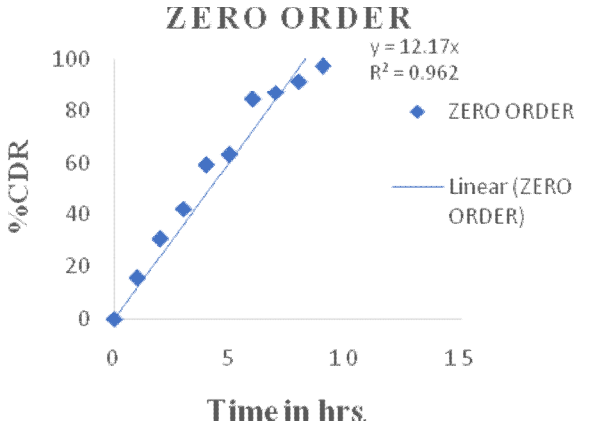


Fig.no 4Percentage Drug Release Profile Combination of Optimized Formulation F13

Table no 8: Kinetics modelling of optimized formulation F13

Formulation code	Zero order (R^2)	First order (R^2)	Higuchi (R^2)	Kores Meyers -peppas (R^2)	N
F13	0.9908	0.9702	0.9905	0.9904	0.5957



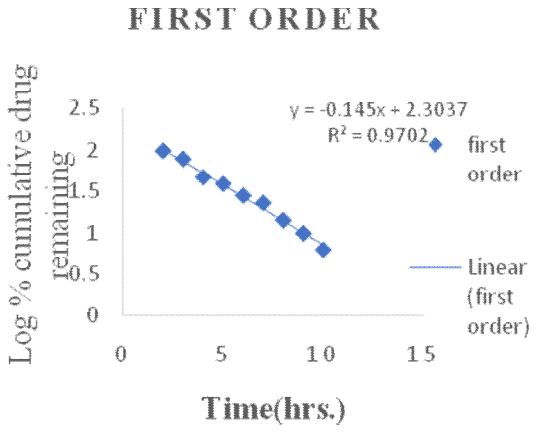


Fig.no 5 - zero order profile Fig no 6 - First order profile

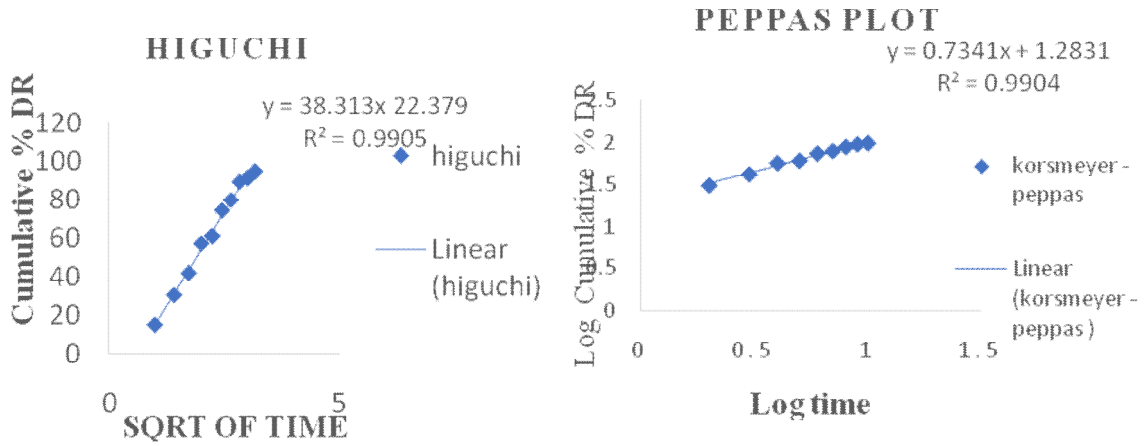


Fig no 6: Higuchi order profile Fig no 8: Koresmeyer's –peppas order profile

Table no 9: Evaluation of Drug content and Evaluation of Invitro drug release studies

Formulation code	Drug content After 1st Month	Drug content After 5 months	Formulation code	% Cumulative drug release (after 10hr) 1st month	% Cumulative drug release (after 10hr) After 5 months
F1	97.25	97.12	**F1**	89.63	89.33
F7	97.48	97.34	**F7**	84.48	84.28
F13	99.81	99.79	**F13**	94.78	94.58

DISCUSSION

The present study anticipates to formulate & evaluate sustained release tablet containing Oseltamivir phosphate, an antiviral drug matrix tablets were successfully prepared by wet granulation method. Formulations F1 to F6 were prepared using hydrophilic polymers HPMC K15 and HPMC E50 in three different ratios 1:0.25,1:0.5 and 1:1. Similarly formulations F7 to F12 were formulated using hydrophobic polymers namely Eudragit and Ethyl cellulose in the ratios of 1:0.25,1:0.5 and 1:1.The physiochemical evaluation results for the granules blend of all trials pass shows the flow properties and compression properties and are of uniform density (i.e. bulk density, angle of repose, hausner's ratio, carr's index). The prepared tablets were also evaluated for post compression properties such as thickness, hardness, weight variation, friability, drug content was found within the limits. Dissolution studies was carried out in 0.1N HCL in initial 2hrs and then in 6.8 pH phosphate buffer showed polymers concentration has great influence on the release of the drug. With increase in the concentration of polymers HPMCK15 and EUDRAGIT RL 100 the drug release increased. Formulation F1 having drug polymer ratio 1:0.25 exhibited a better release (89.63%) comparable to F4 (87.11%) at 8hrs of time. formulation F7 (84.48%) better drug release comparable to F10 (86.17%) at 8hrs of time having a similar drug polymer ratio. By increasing the polymer concentration of the matrix tablet caused an increase in viscosity of the tablet matrix gel layer, with a gel layer is of longer diffusional path. Because of this phenomenon if it is decreased in diffusion of the drug so drug released rate is also decreased [18] With drug is near to matrix surface it might be released before the surrounding polymer caused to reach the polymer disentanglement concentration (no polymer–polymer interactions in a fully hydrated concentration state of the polymer)because the diffusion coefficients for drug molecules were higher than the polymer [16]. Combined effect of polymers on drug release profile was attempted taking HPMCK15 and Eudragit in the ratio of 1:1(F13). It was observed that this formulation has exhibited prolonged release of drug (94.78%) after 10hr period. This optimized formulation revealed the drug release profile to observe zero order kinetics, follows anomalous (non-Fickian) diffusion, this confirms that the drug release through the matrix was diffusion. Stability studies were conducted for the optimized formulations as per ICH guidelines for a period of 0, 60, 90 days which revealed the stability of the formulation.

CONCLUSION

The purpose-based study was successfully done and the sustained release matrix tablets of Oseltamivir phosphate were prepared with water soluble and water insoluble polymers. Formulations F1 to F6 were prepared using hydrophilic polymers HPMC K15 and HPMC E50 in three different ratios 1:0.25,1:0.5 and

1:1. Similarly formulations F7 to F12 were formulated using hydrophobic polymers namely Eudragit and Ethyl cellulose in the ratios of 1:0.25,1:0.5 and 1:1. The physiochemical evaluation results for the granules blend of all trials pass the flow properties and compression properties and are of uniform density. The prepared tablets were also evaluated the post compression properties such as thickness, hardness, weight variation, friability, drug content was found within the limits. Concentrations of the polymers caused a high impact on the release of the drug. As the release of the drug was found to be decreased with the concentrations of the polymers increased. If the polymer proportion is increased the viscosity of tablet is also increased and matrix gel layer and in addition longer diffusional path is observed in the formation of gel layer. Hence it was found that the tablet was decreased in diffusion of the drug and therefore the drug release rate of the tablet is also reduced. In later stages, penetration due to more fluid, the hydrophilic polymer forms viscous gel layer is expanded considered and acted as effective barrier for drug by diffusion. Gel layer formation was observed in HPMC based formulations as a feature of hydrophilic polymers. When the freely water-soluble drug like Oseltamivir phosphate was incorporated in the matrix of HPMC, provides additional osmotic gradient that enhance the solvent penetration resulting in greater polymers swelling and thickness of the gel layer and hence provided greater sustained effects dosage form that release the drug for prolong length of time and soluble polymer. Eudragit was a hydrophobic polymer and its insoluble in nature caused decreased penetration of the solvent which leads to decrease in the diffusion of the drug molecules from the matrix.The present investigation shows that various grades of Hypromellose at suitable concentration combined with Polyacrylate polymers can be used effectively to modify the release rates in hydrophilic matrix tablets prepared by wet granulation technique. The effect of hydrophilic drug Eudragit with HPMC under study which was successfully developed prevents the burst release effect. Hence, it can be concluded that the combined effect of polyacrylate polymer, i.e., EUDRAGIT RL 100 and extra granular polymer, i.e., HPMC K15M at a suitable concentration produced significant effect on drug release.

REFERENCES

1. Allen L.V., Popovich N.G. and Ansel H. (2010) Pharmaceutical Dosage Forms and Drug Delivery Systems, 9 ed: Lippincott Williams & Wilkins 260-75.
2. Ashish Kumar Gupta, (2010). Formulation and Evaluation of Diltiazem Hydrochloride MatrixTablets Using Natural Polymer, Der Pharmacia Lettre, 2(6):68-75.
3. Ayhan S, Yalcin O, Askin I. (2005). Preparation andInvitro Evaluation of Sustained Release Tablet Formulations of Diclofenac Sodium. Farmaco; 60:171-7.
4. Ashish A. Thatte Rahul J. Kadam. (2011), Development, Validation, And Application Of UV-Spectrophotometric Method for The Determination of Oseltamivir Phosphate in Bulk and Pharmaceutical Dosage Form: Int. Chemtech Res. 3(2) 412-21.
5. Aulton ME. (2005). Pharmaceutics: The Science of Dosage Form Design. 2nd ed, London: Churchill Livingstone; 296-298.
6. Bose. A. (2013) Formulation Development And Optimization Of Sustained Release Matrix Tablet Ind J Pharm Sci 21(2) :201-213.
7. Basak S, Jayakumar R, Lucas Mani (2008). Formulation and Release Behaviour of Sustained ReleaseAmbroxol Hydrochloride HPMC MatrixTablet. Ind J Pharm Sci ;68(5): 594-6.
8. Chaudhari, K. (2013) Formulation Development and Evaluation of Sustained Release Matrix Tablet of Zidovudine. American Journal of Advanced Drug Delivery. 1(5) 691-705.
9. Chavan P, (2011). Design and Evaluation of Once Daily Sustained Release Matrix Tablets of Nicorandil International Journal of Pharmacy and Pharmaceutical Sciences, 3 (2)321- 41.
10. Carla L, Teresa Faucci M, Mercedes Fernandez. A, Josefa A, Antonio M, (2002). Development of Sustained Release Matrix Tablets of Didanosine Containing Methacrylic C &Ethyl Cellulose Polymers. Int J Pharm; 213-21
11. Chandran S., Asghar L.F. and Mantha N.(2008) Design and Evaluation of Ethyl Cellulose Based Matrix Tablets of Ibuprofen with pH Modulated Release Kinetics. Indian J. Pharm Sci 70596-602.
12. Deshmukh. V. N, (2009). Formulation and Evaluation of Sustained Release Metoprolol Succinate Tablet Using Hydrophilic Gums, International Journal ofPharm.TechResearch,1(2), 159-163
13. Dhat S, Aphale S, Bagul U, Tagalpallewar A, Vanshiv S, Shah N.(2011). Effect of Two Different Diluents on Release Profile of Aceclofenac From Sustained Release Matrix Tablets Using Gum Damar As Release Retardant. International Journal of Pharmacy and Pharmaceutical Sciences.3(4):307- 13
14. Diwedi RO, Alexandar A, Chandrasekar MJ. (2012). Preparation and in vitro evaluation of sustained release tablet formulations of metformin HCL. Asian Journal of Pharmaceutical and Clinical Research. 5(1):45-8.
15. Dokoumetzidis A, Macheras P.(2006). A century of dissolution research: from Noyes and Whitney to the bio Pharmaceutics classification system. International journal of Pharmaceutics. 321(1):1-1.
16. Eidus L. Hodgkin. M. (1975) A new isoniazid preparation designed for moderately fast and "fast "metabolizers of the drug. Arzneim -Forsch (Drug.Res.)1077-1080.

17. Gayathri. A (2016). Formulation and Evaluation of Monolithic Matrix Tablets of Ambroxil Hcl world research journal pharma technology; 2454-5546.
18. Hemnani M, Patel U, Patel G, Daslaniya D, Shah A, Bhimani B. (2011); Matrix tablet: A tool of Controlled drug delivery. American Journal of Pharm Tech Research. 1(4):127-43.
19. Mohd Abdul Hadi, (2012): Formulation and Evaluation of Sustained Release Matrix Tablets of Glimepiride Based on Combination of Hydrophilic and Hydrophobic Polymers; journal of Applied Pharmaceutical Science. 02 (06);101-107
20. Saini Nisha (2012): Matrix Tablets: An Effective Way for Oral Controlled Release Drug Delivery Iranian Journal of Pharmaceutical Sciences, 8(3): 165-170.
21. Streubel A, Siepmann J, Bodmeier R. (2003), Floating matrix tablets based on low density foam powder: effects of formulation and processing parameters on drug release. Eur J Pharm Sci. 18(1):37-45.
22. Ward.P. (2005) Oseltamivir (Tamiflu) And Its Potential for Use in An Influenza Pandemic, Journal of Antimicrobial Chemotherapy (Suppl. S1, i5–i21 doi:10.1093/jac/dki018.