WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 18, 1141-1157. Research Article ISSN 2277–7105

BILAYER TABLET OF ARTEMETHER & LUMEFANTRINE TABLETS: DEVELOPMENT AND EVALUATION

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Article Received on
05 Sept. 2018,

Revised on 26 Sept. 2018,
Accepted on 17 October 2018

DOI: 10.20959/wjpr201818-13605

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ABSTRACT

Present work Bi-layered tablet of Artemethar and Lumefantrine were prepared by wet granulation method, using superdisintegrants for immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer. Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Artemethar and Lumefantrine were subjected to hardness, weight variation, friability, drug content uniformity, *in vitro* drug release and drug polymer interaction. FTIR and DSC studies indicated that the drug is compatible with all the excipients. Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters. According to the *in vitro* dissolution profile date one formulation of each layer were selected for bi-layered tablet. IRF2 from immediate release formulations as they showed 96.62% drug release within 20 minute. SRF1 from sustained release formulation as they showed 98.18% drug release within 18 hours. The bilayer tablets were prepared using the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping. The percentage drug content was uniform in all the formulations of prepared bi-layered tablets. *In vitro* drug release pattern of the bi-layered tablets were same as individual layer tablets. The stability study showed that no significant changes in tablets after 3 months' study. Based on the observations, it can be concluded that the formulated bi-layered tablets of Artemether and Lumefantrine using superdisintegrants, release retardant polymers and different excipients was capable of exhibiting all the

properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

KEYWORDS: Antimalarial, Bi-layered tablet, Kinetic Release, Artemether and Lumefantrine.

INTRODUCTION

The oral route of drug administration is the most important method of administering drug for systemic effect. More than 90% of the drugs used to produce systemic effect are administered by the oral route.[1] Different types conventional dosage forms that are administered orally, release the API into the absorption pool immediately. Upon administration of the dosage form the therapeutic plasma concentration is reached very quickly but does not maintain the drug level in the blood for an extended period of time.[2] They have a very short duration of action. The short duration of action is due to inability of conventional dosage form to control temporal delivery. A drug blood level vs. time profile for a conventional dosage form administered orally.[3] To achieve and maintain the concentration of an administered drug within therapeutically effective range, it is often necessary to take drug dosage several times and thus results in a fluctuating drug level in plasma.[4]

The controlled release tablet or bilayer tablet contain immediate release layer which work as loading dose and the sustained release layer will maintain the therapeutic plasma drug concentration for prolonged period of time.[5] In the bilayer tablet immediate release layer provide initial burst of drug release followed by constant release rate of drug for defined period of time.[6] This system is used when maximum relief is needed to be achieved quickly, and it is followed by a sustained release layer to avoid repeated administration. Those drugs which have frequency 2 or more than 2 times per day are best candidates for this type of administration. Example: antihypertensive, antihistaminic, ant diabetic, non-steroidal anti-inflammatory drugs.[7]

Over a thousand deaths per day are exhibited due to malaria in infants and children under five years of age across the world. Despite this, there are no satisfactory World Health Organization (WHO)-endorsed pediatric anti-malarial formulations available including all age groups.[8] Artemisinin-based combination therapy is the current standard of care for patients with uncomplicated falciparum malaria in many African countries.[9] Artemether/Lumefantrine meets WHO prequalification criteria for efficacy, safety and

quality. Coartem®, a fixed dose combination of Artemether and Lumefantrine, has consistently achieved cure rates of >95% in clinical trials.[10] However, AL tablets are inconvenient for caregivers to administer as they need to be crushed and mixed with water or food for infants and young children. Besides, like other antimalarial, they have a bitter taste, which may result in children spitting the medicine out and not receiving the full therapeutic dose.[11] There is a clear unmet medical need for a formulation of Artemether/Lumefantrine specifically designed for infants and children in all age groups.

MATERIAL AND METHOD

Materials: Artemether, Lumefantrine, Lactose, Croscarmellose sodium, Hypromellose, Sodium starch glycolate, Microcrystalline cellulose, Magnesium stearate, Ponceau 4R, Talc, HPMC K4M, HPMC K100M, Microcrystalline cellulose, Magnesium stearate.

Formulation of Immediate release layer

Artemether was prepared by wet granulation by using different Superdisintegrants such as Croscarmellose sodium, Hypromellose and Sodium starch glycolate, MCC was used as adsorbent. Manufacturing Steps-Pass all the ingredients though sieve #80. Mix Artemether with MCC geometrically and then mix with lactose. Add Superdisintegrants and mix for 10 to 15 min in mortar and pestle. Make wet mass using binding agent solution containing colour. Pass the cohesive mass through sieve # 16 to get uniform granules. Dry the granules at 50^0C for 15 min in hot air oven. Lubricate the granules with lubricating agent and compressed into150 mg each tablet weight by adjusting hardness. The formulations are shown on table1

Table. 1: Formulation of immediate release layer (IRF).

S. No.	Ingredients	IRF1	IRF2	IRF3	IRF4	IRF5	IRF6
1	Artemether (DMF Grade)	20	20	20	20	20	20
2	Lactose	70	65	70	65	70	65
3	Croscarmellose sodium	15	17	-	-	5	7
4	Hypromellose	12	15	12	15	12	15
5	Sodium starch glycolate	-	-	25	25	20	20
6	Microcrystalline cellulose	40	40	40	40	40	40
7	Magnesium stearate	6	6	6	6	6	6
8	Ponceau 4R	0.02	0.02	0.02	0.02	0.02	0.02
9	Talc	20	20	20	20	20	20
	Total	200	200	200	200	200	200

Formulation of sustained released layer: Accurately weighed Lumefantrine and polymer and others ingredients were taken in mortar and pestle and mixed well. The powder ware mixed with sufficient quantity for HPMC K4M and HPMC K100M solution until wet mass formed. The cohesive mass obtained was passed though sieve # 16 and the granules were dried in a hot air oven at 500C for 20 min. The dried granules again passed through sieve # 22 to break the large lumps. Then granules were mixed with talc and magnesium stearate and compressed into 300 mg each tablet by adjusting hardness. The formulations were shown on table 2.

Table. 2: Formulation of sustained release layer (SRF).

S. No	Ingredients	SRF1	SRF2	SRF3	SRF4	SRF5	SRF6
1	Lumefantrine	120	120	120	120	120	120
2	Lactose	65	60	65	60	65	60
3	HPMC K4M	55	60	-	-	40	35
4	HPMC K100M	-	-	45	50	15	25
5	Microcrystalline cellulose	40	40	40	40	40	40
6	Magnesium stearate	4	4	4	4	4	4
7	Talc	6	6	6	6	6	6
	Total	300	300	300	300	300	300

Preparation of bi-layered tablet: By the study of disintegration and drug release profile of IRL and SRL, best formulations of each layer were chosen and bi-layered tablet were prepared by double compression in single rotatory tableting machine.[13]

Evaluation of post compression parameters for immediate release layer was done for following parameters.

Weight variation[14]

Weigh individually 20 tablets select at random and calculate the average weight. Not more than two of the individual weights deviate from the average weight.

Hardness[14]: Hardness indicates the ability of a tablet to withstand mechanical shock while handling. Hardness of tablet is determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets are randomly pick from each batch and analyzed for hardness. The mean and standard deviation is also calculated.

Thickness[14]

Tablet thickness was measured by vernier caliper. Tablet thickness was control within a ± 5% variation of standard value. The mean and standard deviation is also calculated.

Friability[14]

Friability of a tablet was determined in laboratory by Roche friabilator. A pre weighed 20 tablets are place in the friabilator. Friabilator consist of a plastic chamber that revolves at 25 rpm. The tablets are rotated in the friabilator for at least 4 minutes. At the end of test, tablets are reweighed, the loss in the weight of tablet is the measured.

Disintegration test (IRF layer)[14]

The test is carry out using the apparatus specified in I.P. 2015 distilled water at 37ºC ± 2ºC is use as a disintegration media and the time in second will take for complete disintegration of the tablet with no pallable mass remaining in the apparatus is measure in seconds. Three trials for each batch and the standard deviation were also determined.

***In-vitro* dissolution studies of immediate release layer**[15]

The in-vitro dissolution studies were performed using USP-II (paddle) dissolution apparatus at 100 rpm. Phosphate buffer pH 6.8 dissolution media is maintained at 37±0.500C. A 5 ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analysed on UV Spectrophotometer at 210 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated.

***In vitro* dissolution studies of sustained release layer**[15]

The in vitro release of sustained release layer was carried out for 18 hours using USP type II apparatus (DT-1200) at 100 rpm for the first 45 minute in 900 ml 0.1N HCL maintaining at 37 ±0.50C and then at phosphate buffer pH 4.5 in 900ml for another 18 hour. A 5 ml was withdrawn at different time intervals and replaced with an equal volume of fresh medium. The samples were suitably diluted with blank dissolution medium, filtered and analyzed on UV spectrophotometer at 310nm.

Drug Content for IRF, SRF and Bi-layered tablet[16]

Ten tablets were weight and average weight is calculated. All tablets were crushed and powder equivalent to 100 mg drug was dissolved in pH 6.8 phosphate buffer and the volume was made up to 100 ml with pH 6.8 phosphate buffer. The solution was kept in sonicator for 1 hr. From the stock solution, 1ml solution was taken in 10 ml volumetric flask and the volume was made with pH6.8 phosphate buffer. Solution was filtered and absorbance was measured.

Mathematical modeling of drug release profile[17]

The cumulative amount of Bilayered tablet release from the formulated tablets at different time intervals were fitted to Zero order kinetics, first order kinetics, higuchi model and korsmeyer-peppas model to characterize mechanism of drug release.

Stability Studies[18]

The optimized formulation was subjected for two-month stability study according to standard guidelines. The selected formulations were packed in aluminium foils, which were in wide mouth bottles closed tightly. They were stored at 400C / 75% RH for 3 months and evaluated periodically.

Accelerated stability Studies

The stability study was carried out on the optimized formulation. The sample of tablets was wrapped in the laminated aluminium foil and it was placed in the accelerated stability chamber at 40 ˚C/75% relative humidity for a period of one month. Sampling was done at a predetermined time interval of 0,15 and 30 days. The tablets were evaluated for different physicochemical parameters viz. weight variation, hardness, drug content, in-vitro dissolution study and % swelling index at 8 hrs.

RESULT AND DISCUSSION

Infra-red Spectrophotometric analysis

The pellets were made with mixing 1gm of drug and 100gm of dried potassium bromide powder. Mixer was then compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The thin pallet was put on pellet disc to get IR Spectra.

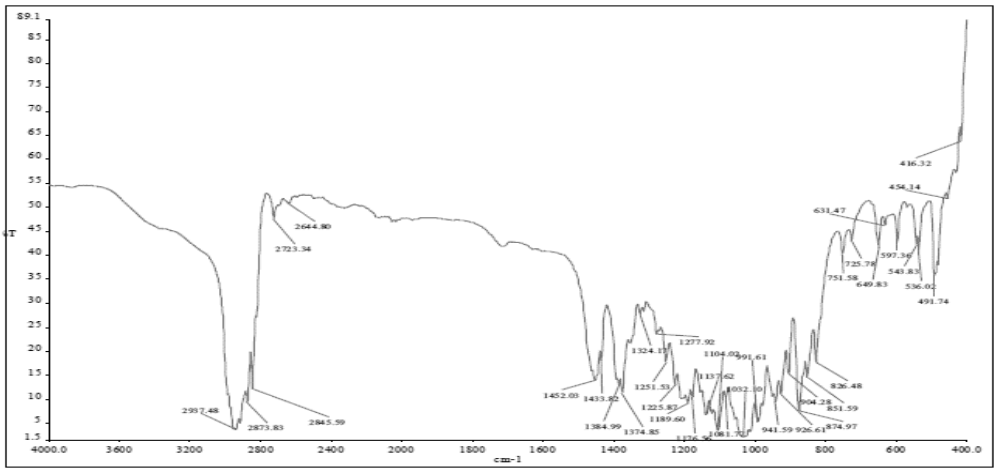

Fig. 1: FTIR Artemether.

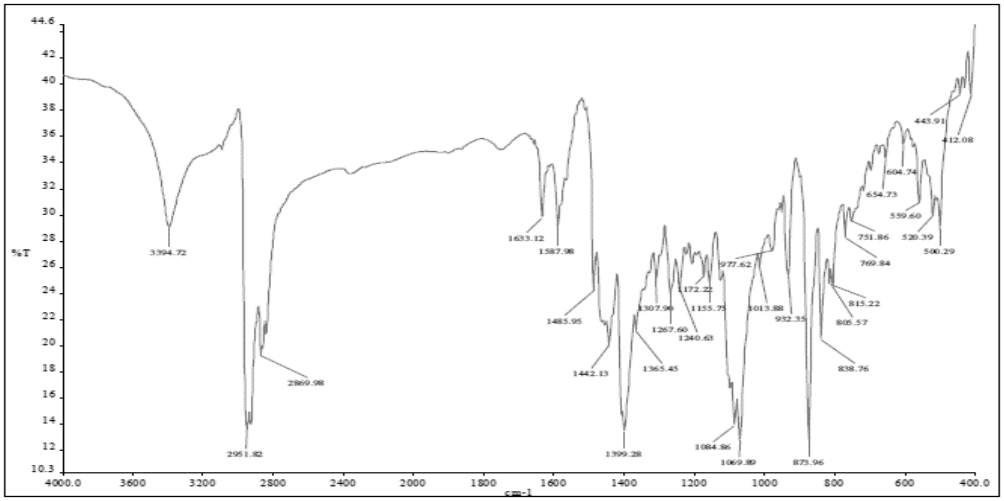

Fig. 2: FTIR Artemether with Excipients.

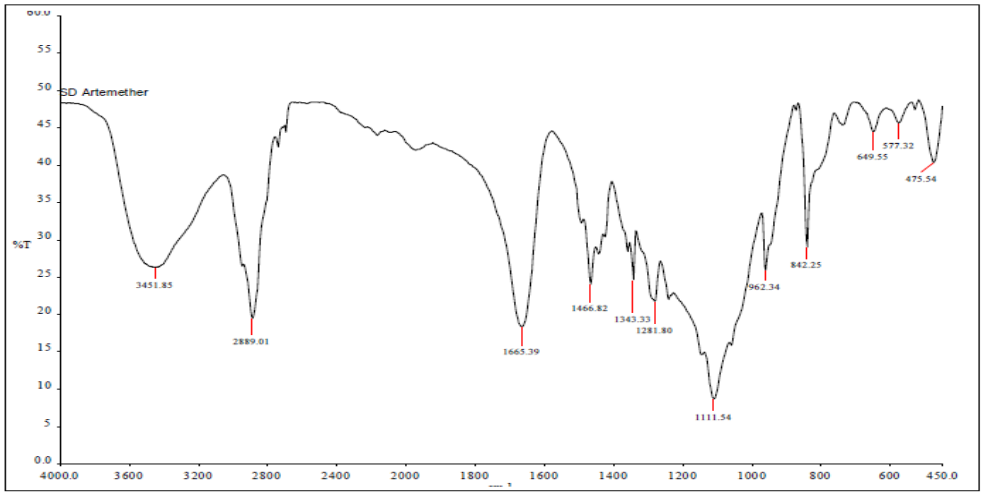

Fig. 3: FTIR Lumefantrine.

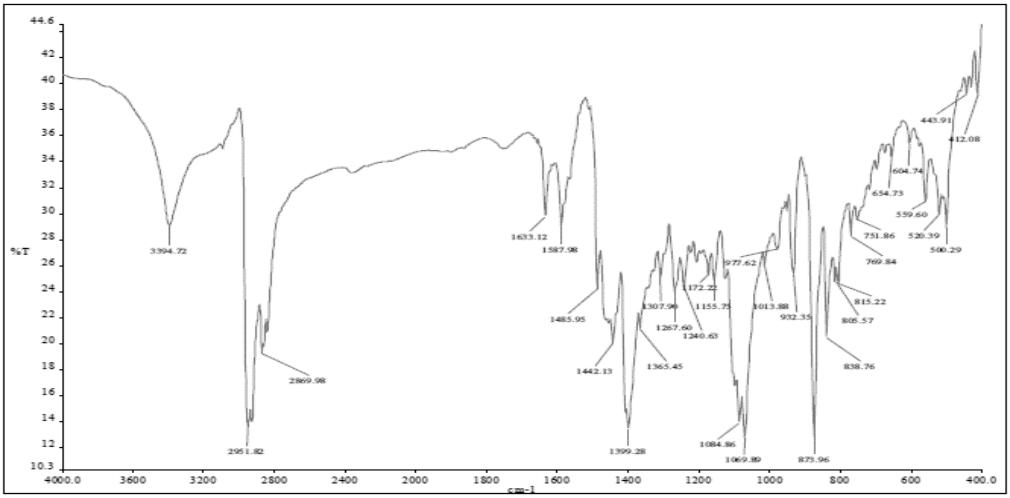

Fig. 4: FTIR Lumefantrine with Excipients.

Differential scanning calorimetry Analysis

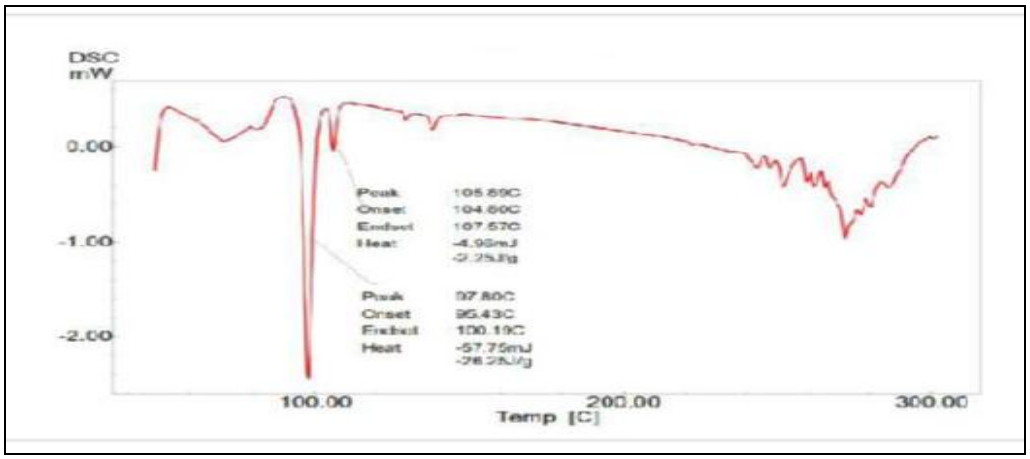

Fig. 5: DSC spectrum of Artemether.

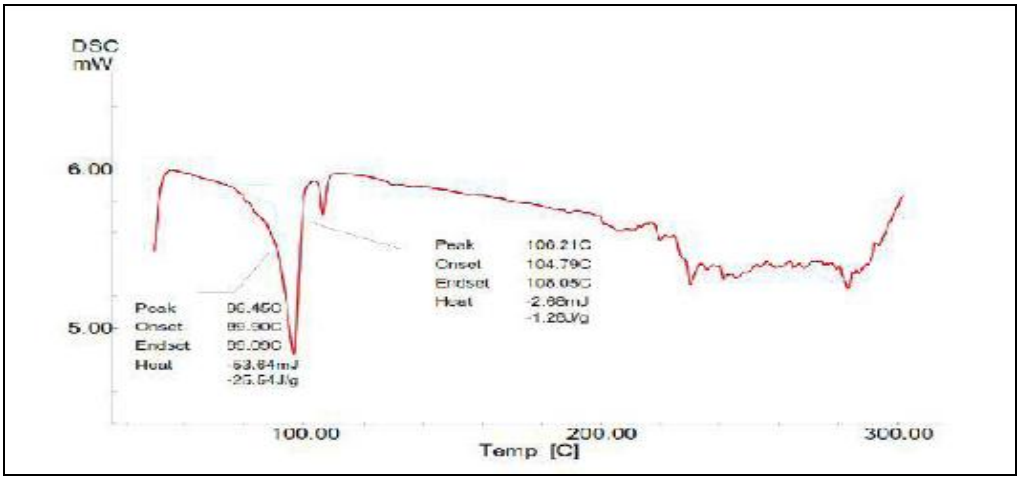

Fig. 6: DSC Spectrum of Lumefantrine.

Pre-compression parameters for IRL and SRL

Table. 3: Pre-compression parameters for IRL and SRL.

Formulation code	Bulk Density Mean ± SD	Tapped Density Mean ± SD	Carr's Index Mean ± SD	Hausner Ration Mean ± SD	Angle of Repose Mean ± SD
IRF1	0.557±0.002	0.637±0.005	12.610±0.217	1.145±0.030	6.596±0.356
IRF2	0.556±0.005	0.655±0.004	15.084±0.226	1.174±0.020	18.360±0.275
IRF3	0.523±0.004	0.626±0.003	15.773±0.109	1.164±0.022	19.421±0.173
IRF4	0.585±0.003	0.684±0.003	13.899±0.177	1.163±0.013	20.147±0.156
IRF5	0.612±0.010	0.682±0.007	11.767±0.206	1.133±0.009	17.913±0.039
IRF6	0.666±0.004	0.755±0.006	11.148±0.157	1.142±0.025	17.101±0.077
SRF1	0.591±0.008	0.694±0.003	13.779±0.206	1.154±0.009	19.604±0.279
SRF2	0.591±0.008	0.699±0.002	14.494±0.328	1.169±0.017	18.480±0.063
SRF3	0.605±0.004	0.681±0.003	11.223±0.186	1.133±0.009	18.201±0.088
SRF4	0.623±0.005	0.703±0.002	11.531±0.127	1.132±0.010	22.548±0.280
SRF5	0.596±0.004	0.710±0.004	16.144±0.249	1.200±0.028	18.331±0.077
SRF6	0.591±0.004	0.727±0.002	18.716±0.397	1.256±0.029	18.168±0.104

Post-Compression Evaluation Parameters

Table. 4: Post-compression parameters for IRL and SRL.

Formulation code	Weight Variation Mean ± SD	Hardness (kg/cm2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug Content (%)Mean ± SD	*In vitro Disintegration* time (sec) Mean ± SD
IRF1	200.9±1.57	5.92±0.05	0.73±0.09	2.86±0.04	98.14±1.19	121.33±1.52
IRF2	200.3±1.60	4.17±0.10	0.48±0.04	2.92±0.10	97.64±1.82	92.66±2.08
IRF3	210.9±1.60	6.25±0.03	0.26±0.06	2.92±0.07	98.63±1.28	73.20±2.51
IRF4	205.55±1.99	6.18±0.07	0.55±0.05	2.86±0.03	99.62±0.94	48.32±3.05
IRF5	200.45±2.52	4.15±0.04	0.62±0.03	2.93±0.06	99.33±1.32	59.32±2.08
IRF6	200.05±1.81	4.52±0.11	0.68±0.04	2.85±0.09	99.54±1.81	37.33±1.54
SRF1	302.6±1.41	5.37±0.10	0.31±0.06	3.33±0.09	99.38±1.19	-
SRF2	302.9±2.29	4.23±0.02	0.34±0.02	3.32±0.14	98.62±1.03	-
SRF3	302.5±1.59	6.13±0.04	0.42±0.03	3.32±0.03	97.40±1.27	-
SRF4	301.75±1.14	6.13±0.06	0.34±0.02	3.27±0.05	98.57±0.80	-
SRF5	300.65±1.37	5.15±0.03	0.42±0.06	3.34±0.06	98.44±1.26	-
SRF6	302.30±1.31	4.22±0.02	0.47±0.03	3.32±0.03	97.63±0.62	-

Post-compression parameters for bi-layered tablet

Table. 5: Post-compression parameters for bi-layered tablet.

Formulation code	Weight Variation Mean ± SD	Hardness (kg/cm2) Mean ± SD	Friability (%) Mean ± SD	Thickness Mean ± SD	Drug Content (%)Mean ± SD
BT	540.75±0.46	7.03±0.15	0.37±0.01	6.25±0.14	99.13±0.53

***In-vitro* dissolution study of IRL**

Table. 6: *In-vitro* dissolution study of IRL

Time in min	IRF1	IRF2	IRF3	IRF4	IRF5	IRF6
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
1	17.057±0.613	21.225±0.871	20.846±0.451	26.531±1.305	30.322±1.124	36.007±1.173
3	31.805±1.075	31.908±1.280	33.738±2.620	54.965±2.391	56.561±0.778	60.653±2.255
5	53.454±2.280	56.489±2.100	56.488±1.288	68.244±0.593	64.455±2.346	68.247±1.723
10	64.847±2.481	70.221±3.001	68.260±1.176	81.535±0.896	77.725±1.791	83.434±2.060
15	71.105±1.634	82.111±1.913	74.131±1.523	89.819±1.107	81.563±0.873	84.918±1.314
20	80.409±1.038	96.625±0.722	82.675±0.582	94.819±0.788	87.245±1.865	85.675±0.582
25	86.676±1.427	98.827±1.427	90.280±1.281	97.497±0.931	92.376±1.325	88.280±1.281
30	91.047±2.031	99.404±1.162	93.135±0.852	98.075±1.265	96.743±1.731	90.135±0.852

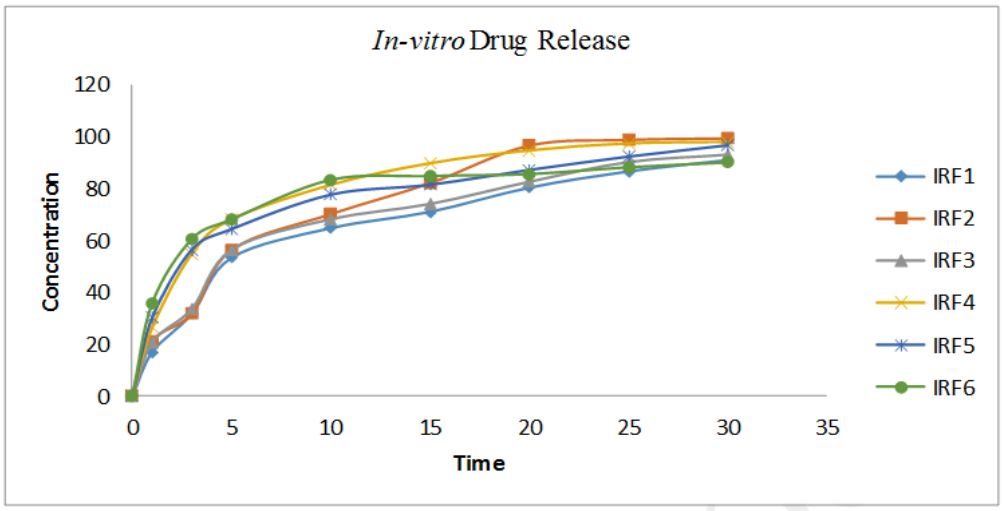

Fig. 7: *In-vitro* dissolution study of IRL.

***In vitro* dissolution study of SRF**

Table. 7: *In-vitro* dissolution study of SRF.

Time in min	SRF1	SRF2	SRF3	SRF4	SRF5	SRF6
0	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000	0.000±0.000
60	15.408±1.222	7.905±1.234	6.017±1.508	13.469±1.222	6.741±1.281	5.558±1.591
120	25.635±1.764	19.265±1.532	18.232±1.281	25.636±0.732	18.524±1.421	12.634±0.751
240	34.323±2.615	24.503±1.083	23.094±1.547	33.236±1.164	25.279±1.003	17.697±1.151
360	42.342±0.632	31.362±1.321	29.735±0.941	38.852±1.521	33.852±1.835	25.742±1.427
480	57.151±1.196	43.142±1.974	36.935±1.251	56.674±2.061	47.993±0.539	33.733±2.378
600	62.343±0.412	48.234±0.826	43.752±1.423	62.316±1.839	50.491±0.694	39.513±1.114
720	76.620±1.642	56.262±2.227	54.963±2.137	70.315±2.001	65.327±1.779	47.031±1.480
960	98.183±0.352	82.430±1.267	66.957±1.402	87.123±0.645	86.183±0.467	54.439±2.565
1080	99.514±1.094	97.816±0.630	84.113±1.316	99.212±1.325	97.693±0.845	67.057±1.192

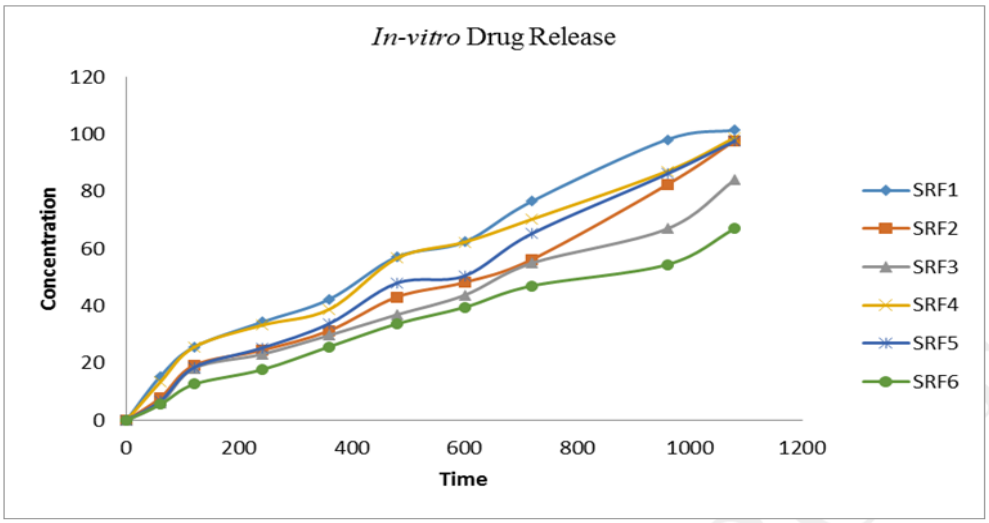

Fig. 8: *In-vitro* dissolution study of SRF.

Dissolution study of Bi-layered Tablet

Table 8: Dissolution study of Bi-layered Tablet

Time in min	% CDR	
	BLT	
	IRF	SRF
0	0.000±0.000	0.000±0.000
10	83.524±1.063	-
20	98.451±1.147	-
30	99.513±0.731	-
60	-	6.384±1.032
120	-	17.612±0.853
240	-	23.483±1.520
360	-	36.154±0.638
480	-	46.054±0.825
600	-	52.854±0.841
720	-	64.771±0.527
960	-	76.14±0.952
1080	-	95.83±0.614

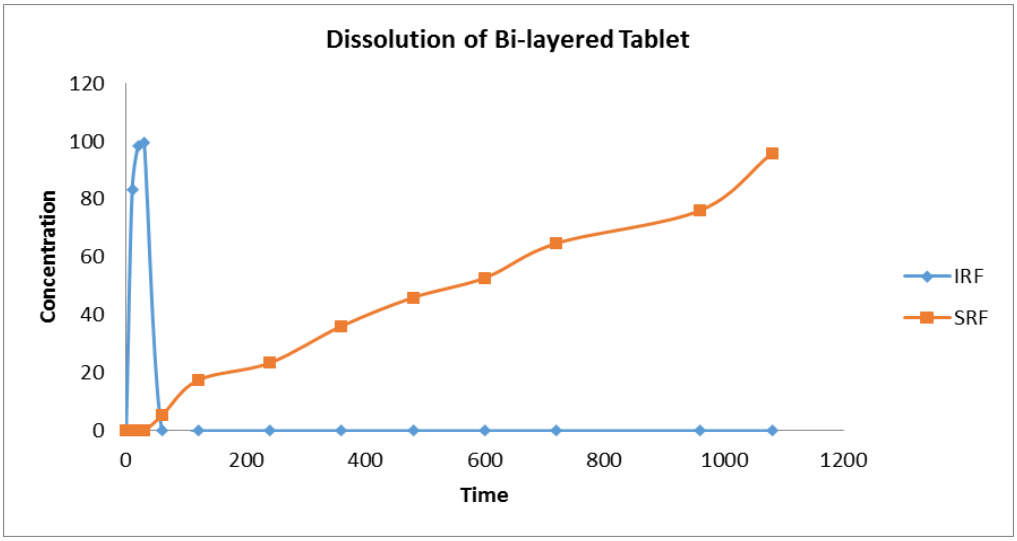

Fig. 9: Dissolution of Bi-layered Tablet.

Release Kinetic for Immediate Release Tablets

Table. 9: Kinetic release for IRF.

Formulation Code	Kinetic Models				
	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer N	R^2
IRF1	0.8363	0.9815	0.9689	0.8915	0.6657
IRF2	0.8227	0.9874	0.9677	0.8695	0.6263
IRF3	0.8232	0.9879	0.9643	0.8712	0.6336
IRF4	0.7068	0.9860	0.9059	0.8424	0.5643
IRF5	0.7105	0.9606	0.9055	0.8040	0.5135
IRF6	0.6834	0.9792	0.8945	0.8033	0.5128

Release Kinetic for Sustain Release Tablets

Table 10: Kinetic release for SRL

Formulation Code	Kinetic Models				
	Zero Order R^2	First Order R^2	Higuchi R^2	Korsmeyer N	R^2
SRF1	0.9822	0.8296	0.9653	0.6548	0.9974
SRF2	0.9837	0.7303	0.9073	0.6426	0.9794
SRF3	0.9836	0.8986	0.9297	0.6256	0.9699
SRF4	0.9734	0.7728	0.9794	0.6511	0.9984
SRF5	0.9918	0.8965	0.9404	0.6571	0.9737
SRF6	0.9847	0.8965	0.9517	0.6065	0.9691

To know the drug release kinetics from these formulations, the dissolution data were subjected to different kinetic model such as Zero order and Higuchi's square root kinetics model. The line of equations and regression coefficient of kinetic study for all the formulations are shown in Table 9 and 10. The regression coefficient was considered as main parameter to interpret release kinetics.

Stability Studies

Stability of a drug can be defining as the time from the date of manufacture and the packaging of the formulation[17], until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously. In any design and evaluation of dosage forms for drugs, the stability of the active component must be a major criterion in determining their acceptance or rejection.

Accelerated stability studies as per ICH guidelines

The optimized formulation Bilayer Tablet (BT) was wrapped in aluminium foils and kept in Petri-dish at (400C±2^{0}C/75% RH ±5%) in humidity chamber. The stability studies were conducted after15 and 30 days.[18]

Table. 11: Accelerated stability data

Stability period	40^0C / 75% RH				
	Hardness Mean ± SD	% Friability Mean ± SD	% Drug content Mean ± SD	Drug release	
				IRL (30 min)	SRL (1080 min)
Initial	7.04±0.67	0.35±0.01	99.13±0.532	99.423	95.723
1 Month	7.08±0.49	0.43±0.03	99.4s5±0.751	99.481	95.321
2 Month	6.45±0.49	0.56±0.06	98.86±0.792	99.242	94.736
3 Month	5.32±0.60	0.74±0.03	96.84±0.921	98.738	94.481

The bi-layered tablets were subjected to short term stability study, storing the formulation at 40^0C / 75% RH for 3 months. The data for stability studies revealed that no considerable differences in physical parameters, drug content and *in vitro* drug release rate were observed.

DISCUSSION

In the present work, formulation and evaluation of bi-layered tablet of Artemether & Lumefantrine tablets was carried out. In this different formulations of immediate release and sustained release layer have been prepared separately. From above formulations best formulation of each immediate and sustained release layers were selected according to the dissolution profile and bilayered tablet were prepared. Bioavailability of 1.18ug/ml and 0.44ug/ml respectively. Artemether has rapid onset of action and is rapidly eliminated from the body. It is thus thought to provide rapid symptomatic relief by reducing the number of malarial parasites whereas Lumefantrine has a much longer action and is used to clear residual parasites.

Infra-red spectrum of drug and excipients were recorded over KBr disc method and obtained spectra were shown in the figure 5.3 to 5.6. All the characteristic peaks of Artemethar and Lumefantrine were present in the spectrum of drug and excipient mixture, indicating compatibility between drug and excipients. The spectrum confirmed that there is no significant change in the chemical integrity of the drug. There is no change in functional group peaks (Aliphatic C-H stretch, C-H bend, C-H stretch, O-H bend and Carboxylic acid) of Artemethar and Lumefantrine. The DSC thermogram of Artemethar and Lumefantrine exhibits a sharp endothermic peak at 97.8^0C within the range 1.0^0C indicating the sample is in the pure form. The peak of formulation containing SSG, CS, HPMC K4M and HPMC K100M showed a wide range of melting process which has started at around 90^0C and completed at around 99^0C with a range 9^0C suggesting that drug in the formulation had remained in an unreacted form. The excipients along with drug in formulation were responsible for prolonged melting range of the formulation. It indicates that it may not affect the stability of formulation, so it is confirmed that drug is compatible with all excipients. Both immediate and sustained release formulations were prepared by wet granulation method. Six batches (IRF1-IRF6) of immediate release layer and six batches (SRF1-SRF6) of sustained release layer were developed by altering the excipients ratio as given in table 1 and table 2 respectively. Immediate release tablet were prepared by using superdisintegrants such as sodium starch glycolate and croscarmellose sodium and Sustained release tablet were

prepared by using polymer like HPMC K4M and HPMC K100M. The tablets were evaluated for weigh variation, friability, thickness, drug content and *in vitro* dissolution parameters using standard procedure as shown in Table 5. Best formulations for preparation of bi-layered tablet were selected depending upon the dissolution profile as all the formulation showed good content uniformity, friability, hardness and other physical parameters.

Pre-formulation studies were carried out for all the formulation. Powder properties such as angle of repose, carr's inderx, hausner's ratio, bulk density, tapped density were determined which shown on tablet 3. Pre-formulation studies for the formulations depicted bulk density 0.556 to 0.666 gm/cm^3 which indicated packing characteristics in dies. The carr's compressibility index was found to be below 18% which suggested good compressibility of blend. The values of hausner ratio and angle of repose were found in the range of 1.13 to 1.25 and 16.59^0 to 22.54^0 respectively suggested excellent flow property of powder blend. Though the batch size of formulations were limited to 50-80, weight variation was reasonably satisfying the IP Limits as given in table 4.7 and the drug content uniformity of all formulations was found to be 97.40-99.62 which indicated uniform distribution of drug in all batches of the formulations. Further hardness and friability was also between 4-6 kg/cm^2 and less 1% respectively indicating stability of tablets against physical shocks.

In vitro drug release profile of the immediate release and sustained release formulations were given in table 6 and 7 respectively. Among all formulations of immediate release layer, formulation IRF1, IRF3, IRF4 IRF5 and IRF2 showed the least drug release 80.40, 82.67, 94.81, 87.24, 85.67 and 96.62 respectively in 20 min. Formulation IRF2 releases 96.2% drug in 20 min. The release profile of the formulation IF2 was believed be due to combination of Croscarmellose sodium and Hypromellose. The result indicated that increase in the concentration of superdisintegrants and combination of superdisintegrants increases the release profile of drug. In sustained release formulation, the formulation SRF1 (18% HPMC K4M) showed highest release in 16 hours compare to the formulations SRF2. The formulations SRF3 and SRF4 containing 15% and 16.6% of HPMC K100M showed 84.11 and 98.18% drug release in 18 hours. SRF1 was selected as best sustained release formulation based on dissolution profile as they showed more than 90% after 18 hours. The formulations found to contain combination of HPMC K4M and HPMC K100M in ratio 1:1 of the concentration 17.5% of total weight. The selected formulation of immediate and sustained release layer was prepared as bilayered tablet and the post-compression parameters tabulated

in 5.6. Hardness and friability showed 7.05±0.15 and less than 1% respectively indicating the stability against physical stokes. Thickness was found to be 6.25±0.14 mm and content of uniformity 99.44±0.55 indicate uniform distribution of drug in both layer. In vitro drug release showed in table 8. The release pattern of the drug from bi-layered tablet showed same as the individual layer tablets of immediate and sustained release.

The release kinetics of immediate release layer formulations (IRF1-IRF6) was found to following clearly first order kinetics as the values for 'r' is (0.985 to 0.960) and values of 'n' is more than 0.89 shown that Super case II transport. The release kinetics of sustained release layer (SRF1-SRF6) was found to following zero order kinetics as the value for 'r' is (0.9918 to 0.9736) found to be high in comparison to first order (0.8986 to 0.7303) and Higuchi's square root of time (0.9794 to 0.9074). 'n' values in between 0.6634 to 0.6064 shown non-fickian release. Stability studies at 40^0C / 75% RH for 3 months for bi-layered tablet tabulated in table 5.12 showed that there is no significant loss in drug content, hardness and also no any changes in physical appearance within 2 month of the stability period. But there was slightly change in the hardness and drug content of uniformity in 3-month period stability data which indicates that special care during the storage condition. In *in vitro* drug release pattern no significant change than the initial period.

CONCLUSION

In the present work bi-layered tablet of Artemethar and Lumefantrine were prepared by wet granulation method, using superdisintegrants such as sodium starch glycolate and croscarmellose for immediate release layer and polymer like HPMC K4M and HPMC K100M for sustained release layer.

Best formulations of each layer were selected for bi-layered tablet and bi-layered tablet were prepared. Bi-layered tablet of Artemethar and Lumefantrine were subjected to hardness, weight variation, friability, drug content uniformity, *in vitro* drug release and drug polymer interaction. FTIR and DSC studies indicated that the drug is compatible with all the excipients. Both immediate and sustained release layer were prepared by wet granulation method and punched separately. The prepared tablets of both layers were evaluated for post compression parameters. According to the *in vitro* dissolution profile date one formulation of each layer were selected for bi-layered tablet. IRF2 from immediate release formulations as they showed 96.62% drug release within 20 minute. SRF1 from sustained release formulation as they showed 98.18% drug release within 18 hours. The bilayer tablets were prepared using

the selected immediate and sustained release layer. The prepared tablets were found to be good and free from chipping and capping. The hardness of the prepared tablets was found to be in the range of 5.85 to 7.05 kg /cm^2 The low values of the standard deviation of average weight of the prepared tablets indicate weight uniformity within the batches prepared. The friability of the prepared tablet was found to be less than 1%. The percentage drug content was uniform in all the formulations of prepared bi-layered tablets. *In vitro* drug release pattern of the bi-layered tablets were same as individual layer tablets. The stability study showed that no significant changes in tablets after 3 months study. Based on the observations, it can be concluded that the formulated bi-layered tablets of Artemethar and Lumefantrine using superdisintegrants, release retardant polymers and different excipients was capable of exhibiting all the properties of bi-layered tablet. They are thus reducing the dose intake, minimize dose related adverse effect, cost and ultimately improve the patient compliance and drug efficiency.

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