MANTECH Publications

Journal of Pharmaceutical Chemistry and Drug formulation
Volume 4, Issue 2, May-August, 2022

Formulation and Assessment of Rapidly Dissolving Artemether and Lumefantrine Tablets

Sourav Vashisht[1], Piyush Saxsena[2]

Professor, Student[2]

Department of Pharmaceutics

B.S.R. College of Pharmacy

Corresponding Author's Email: - *piyushsaxsena112@gmail.com[2]*

Abstract

Artemether and lumefantrine are antimalarial medications used to treat malaria. The proposed study activity will create and analyse fast dissolving tablets (FDTs) of artemether and lumefantrine, which will avoid first-pass metabolism, improve dissolve rate, and increase bioavailability. Fast dissolving tablets (FDTs) were prepared via direct compression using a combination of superdisintegrants such as Crosspovidone and sodium starch glycolate (5%, 10%, and 15%) and evaluated for physicochemical evaluation parameters such as hardness, friability, weight variation, drug content uniformity, water absorption ratio, wetting time, in-vitro andisintegration time, and in-vitro dissolution studies. The control tablet (no superdisintegrant) was developed and tested. F1 through F6 formulations were developed, with F3 (crosspovidine) being the most optimised. The hardness, friability, weight fluctuation, and drug content were all determined to be within pharmacopoeia standards. The improved formulation, F3, had a water absorption ratio of 62.87%, a wetting time of 12 seconds, and an in-vitro disintegration time of 15 seconds. F3 was deemed the best formulation, releasing up to 99.49% (artemether) and 99.15% (lumefantrine) after 25 minutes. The best formulation, F3, was used to compare the dissolving rate profile of formulation and controlled formulation of artemether and lumefantrine tablets. The formulation, F3, demonstrated entire drug release in 25 minutes, while the controlled formulation demonstrated 26.50% (artemether) and 24.50% (lumefantrine) drug release in 25 minutes. The best formulation, F3,

was also subjected to a stability analysis, which revealed that there was no significant change in any parameters. As a result, the formulation F3 was deemed extremely stable.

Keywords: *Water Absorption Ratio, Fast Dissolving Tablets, Wetting Time, In-Vitro Dissolution Studies, Stability Studies*

INTRODUCTION

The desire to provide patients with more traditional methods of taking their medication led to the development of the fast dissolving drug delivery system. Many people have trouble swallowing medications and thick gelatin capsules. As a result, they do not follow the prescription, resulting in a high rate of noncompliance and unsuccessful therapy.

The current study attempted to formulate fast dissolving tablets of arthemether and lumefantrine using superdisintegrants such as sodium starch glycolate and crosspovidine. The effect of different superdisintegrants on various tablet parameters was studied, and functionality differences were evaluated. The goal of this study was to improve drug molecule efficacy, achieve better compliance, improve onset of action, and provide a stable dosage form.

The aim of this study was to enhance the efficacy of drug molecule, achieve better compliance, enhance onset of action, and provide stable dosage form[13].

MATERIALS AND METHODS

Arthemether and lumefantriene was Gifted by Hetro drugs., Hyderabad, B-cyclodextrin Crosspovidine, Sodium Starch glycolate, Anhydrous sodium bicarbonate & Light magnesium carbonate was gifted by Nikitha chemicals, India, Mannitol, Aspartame, Aerosil, Talc, Magnesium stearate was gifted by Vasundhara rasayans ltd, India.

UV Spectrophotometric Analysis:

Preparation of standard stock solution

50mg of artemether transferred into 50ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with phosphate buffer 6.8. This gives stock solution of concentration (100mg/ml), from this 5ml was withdrawn and diluted to 50ml to get a concentration of (10mg/ml)[4].

Standard curve preparation of Artemether

From this standard solution stock solution, aliquots 1,2,3,4,5,10ml were withdrawn and made up to 10ml phosphate buffer 6.8 to give a concentration of 1, 2, 3, 4, 5, 10mg/ml. Absorbance of these solution was measured 254nm[5].

Preparation of standard stock solution

50mg of lumifantrine transferred into 50ml volumetric flask. It was dissolved in methanol and volume was made up to the mark with phosphate buffer 4.5. This gives stock solution of concentration (100mg/ml), from this 5ml was withdrawn and diluted to 50ml to get a concentration of (10mg/ml).

Standard curve preparation of lumefantrine

From this standard solution stock solution, aliquots 1,2,3,4,5,10 ml were withdrawn and made up to 10ml phosphate buffer 4.5 to give a concentration of 1, 2, 3, 4, 5, 10mg/ml. Absorbance of these solution was measured 315nm. The results were mentioned in the table. No: 2 - 3

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[6].

The results were mentioned in the Figure. No: 1 - 5

Preformulation Studies

Preformulation study relates to Pharma--ceutical and analytical investigation carried out proceeding and supporting formulation development efforts of the dosage form of the drug substance. Preformulation yields basic knowledge necessary to develop suitable formulation for the toxicological use. It gives information needed to define the nature of the drug substance and provide frame work for the drug combination with pharmaceutical excipients in the dosage form[7].

Bulk Density (Db), Tapped Density (Dt), Angle of Repose (θ), Carr's index (or) % compressibility and Hausner ratio The results were mentioned in the table. No: 4

MANUFACTURING METHOD

Table No.1: Formulation of fast dissolving tablet

Sr.no	Ingredients	F0	F1	F2	F3	F4	F5	F6
1	B-cyclodextrins	240	240	240	240	240	240	240
2	Sodiumbicarbonate	4	4	4	4	4	4	4
3	magnesium carbonate	7	7	7	7	7	7	7
4	Artemether	20	20	20	20	20	20	20
5	Mannitol	100	95	90	85	95	90	85
6	Aspartame	12	12	12	12	12	12	12
7	Aerosil	8	8	8	8	8	8	8
8	Citric acid	7	7	7	7	7	7	7
9	Crosspovidine	-	5	10	15	-	-	-
10	Sodium starch glycolate	-	-	-	-	5	10	15
11	Talc	2	2	2	2	2	2	2
12	Magnesium stereate	10	10	10	10	10	10	10
	Total weight	410	410	410	410	410	410	410

Evaluation Fast Dissolving Tablets 8-10

Weight variation test:

20 tablets were selected randomly from the lot and weighted individually to check for weight variation. Weight variation specification as per I.P. is shown in the results were mentioned in the table. No: 5

Hardness test:

Hardness or tablet crushing strength (fc), the force required to break a tablet in a diametric compression was measured using Monsanto tablet hardness tester. It is expressed in kg/cm2.

The results were mentioned in the table. No: 5

Thickness

The thickness of tablets was determined suing a Digimatic veriner caliper (Mitutoya, Japan). Three tablets from each batch were used, and average values were calculated.

The results were mentioned in the table. No: 5

Friability (F):

Friability of the tablet determined using Roche friabilator. This device subjects the tablet to the combined effect of abrasion

and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Pre-weighted sample of tablets was placed in the friabilator and were subjected to the 100 revolutions. Tablets were dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F=W_{initial}-W_{final}x100/W_{initial}$$

Acceptance criteria for % friability, %weight loss should be less than 1% The results were mentioned in the table. No: 5

Finished product parameter

Disintegration time testing

It was determine using USP tablet disintegration test apparatus, using 900ml of distilled water without disk at room temperature. Test was performed on 6 tablets. Limit set for the disintegration time: not more than 30 seconds.

The results were mentioned in the table. No: 6

In vitro dispersion time:

For determination of in vitro dispersion time, one tablet was placed in a beaker containing 10ml of PH 6.8 phosphate buffer at 37±0.5ºc and the time required for complete dispersion was determined. The test was repeated on three other tablets of same batch, the average gives in vitro dispersion time

Wetting time of tablet

Wicking time test gives the idea on porosity, compressibility as well as absorption capacity of the tablets. Since the dissolution process of a tablet depends upon the wetting followed by disintegration of the tablet, the measurement of wetting times may be used as another confirmative test for the evaluation of tablets.

Procedure:

For determination of wetting time, piece of tissue paper folded twice was placed in a small Petri dish (internal diameter of 5 cm) containing 6ml of wager. A tablet was carefully placed on the surface of tissue paper. The time required for water to reach the upper surface of the tablets was noted as the wetting time. The test was repeated on the three other tablets of the same batch in same Petri dish and average of the three readings gives then means wetting time of the tablets.

The results were mentioned in the table. No: 7

Water absorption Ratio

A piece of tissue paper folded twice was

placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio, R, was determined using following equation,

R=100(Wb-Wa) /Wa

where, Wa is weight of tablet before water absorption Wb is weight of tablet after water absorption.

ASSAY (ARTEMETHER):

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100mg artemether was shaken with 100ml of 6.8 phosphate buffer in 100ml amber colored volumetric flask and from this 10ml pipette out and dilute upto 100ml.from standard solution again 10ml pipette out and diluted upto 100ml in 100ml amber colored volumetric flask resulting solution was filtered and assayed at 254nm and content of artemether was calculated.

The results were mentioned in the table. No: 5

ASSAY (LUMEFANTRINE):

Twenty tablets from each batch were weighed accurately and powdered powder equivalent to 100mg lumefantrine was shaken with 100ml of 4.5 phosphate buffer in 100 ml amber colored volumetric flask and from this 10ml pipette out and dilute upto 100ml.from standard solution again 10ml pipette out and diluted upto 100ml in 100ml amber colored volumetric flask resulting solution was filtered and assayed at 310nm and content of lumefantrine was calculated.

The results were mentioned in the table. No: 5

In vitro drug release study (artemether):

The release rate of drug from FDT was determined using USP Dissolution testing apparatus II (paddle method). The dissolution medium was 6.8ph phosphate buffer, the volume being 900ml. the temperature was maintained at 37±0.5ºc. The rotation speed was 50rpm.

A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 5,10,15,20 and 25 minutes. And the samples were replaced with fresh dissolution medium. The samples were filtered through a membrane filter and absorbance of these solutions was measured at 254nm using a UV/V is double-beam spectrophotometer of Cumulative percentage drug release was

calculated using linear equation obtained from a standard curve.

The results were mentioned in the Table. No: 5, 8 & 9

In vitro drug release study (lumefantrine):

The release rate of drug from FDT was determined using (USP XXIII) 67 Dissolution testing apparatus II (paddle method). The dissolution medium was 4.5PH phosphate buffer, the volume being 900ml. the temperature was maintained at 37±0.5ºc. The rotation speed was 50rpm. A sample (5ml) of the solution was withdrawn from the dissolution apparatus at 5, 10, 15, 20 and 25 minutes. And the samples were replaced with fresh dissolution medium.

The samples were filtered through a membrane filter and absorbance of these solutions was measured at 310nm using a UV/V is double-beam spectrophotometer of Cumulative percentage drug release was calculated using linear equation obtained from a standard curve.

The results were mentioned in the Table. No: 5, 8 & 9

Stability studies Introductions

Stability of a drug can be define as the time from the date of manufacture and the packaging of the formulation, 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.

Stability Studies 10-11

Stability of a drug can be define as the time from the date of manufacture and the packaging of the formulation, 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.

In the present work stability study was carried out for the optimized formulation at 400C±20C/75%RH±5%RH for three

The results were mentioned in the Table. No: 10-12.

RESULTS AND DISCUSSIONS:

Table No: 2 Standard curve of lumefantrine

Sr.No.	Conc. (mcg/ml)	UV absorbance
1	0	0
2	2	0.125
3	4	0.248
4	6	0.362
5	8	0.486
6	10	0.611
7	12	0.729
8	14	0.850
9	16	0.962
10	18	1.089

Beer-Lambert's law was obeyed over the range and data was found to fit the equation R2=0.9994, Slope=0.058

CONCLUSION

The standard curve prepared shown very linearity hence it was used for further analysis.

Table No: 3 Standard curve of Artemethar

Sr no	Conc (mcg/ml)	ABS (nm)
1	2	0.115
2	4	0.229
3	6	0.338
4	8	0.454
5	10	0.568
6	12	0.675
7	14	0.788
8	16	0.899
9	18	0.998

Beer-Lambert's law was obeyed over the range and data was found to fit the equation R^2=0.9992, Slope=0.055

CONCLUSION

The standard curve prepared shown very linearity hence it was used for further analysis

Infra-Red Spectrophotometric analysis

Using IR spectrometer carried out the analytical studies of the drug and FDT product. The characteristic peaks are listed in the table.IR spectroscopic studies indicated that the drug is compatible with all the excipients.

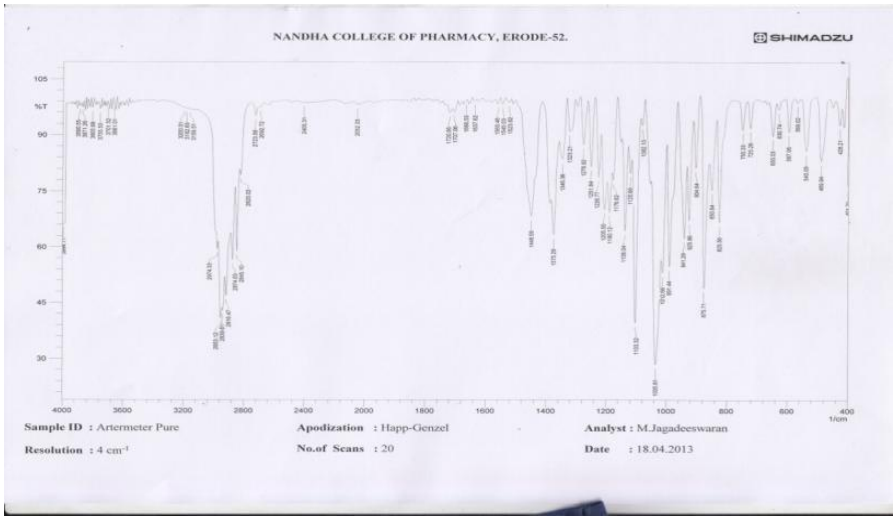

Fig No: 1 IR Spectra of drug (Artemether)

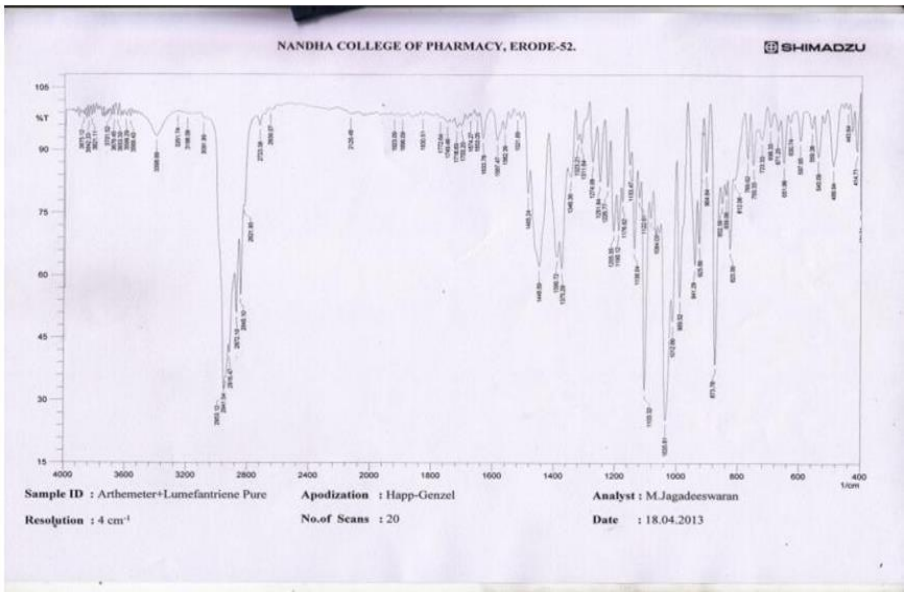

Fig No: 2 IR Spectra of drug (Lumefantrine)

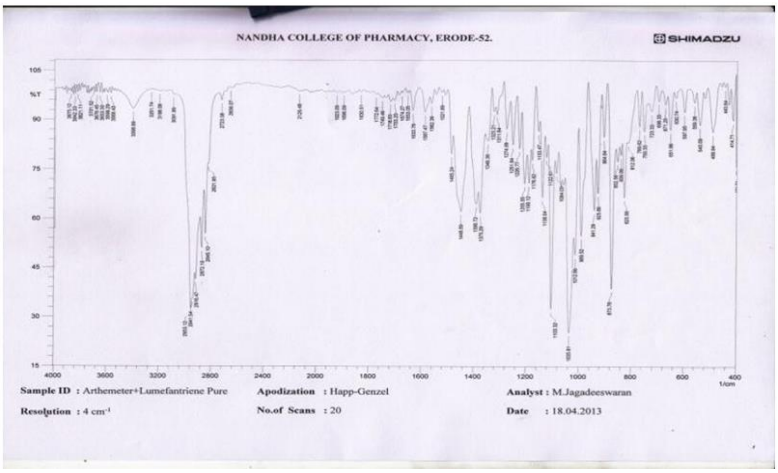

Fig No 3: IR Spectra of drug (Artemether+Lumefantrine)

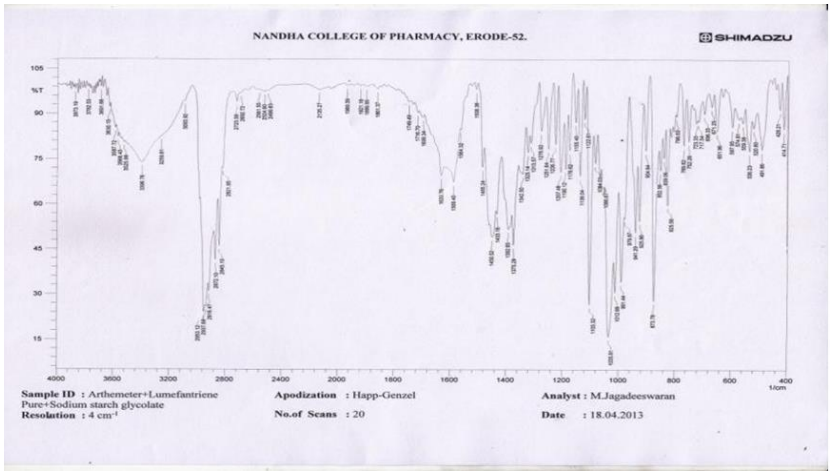

Fig No: 4 IR Spectra of drug (Artemether+Lumefantrine+Sod.Starch Glycolate)

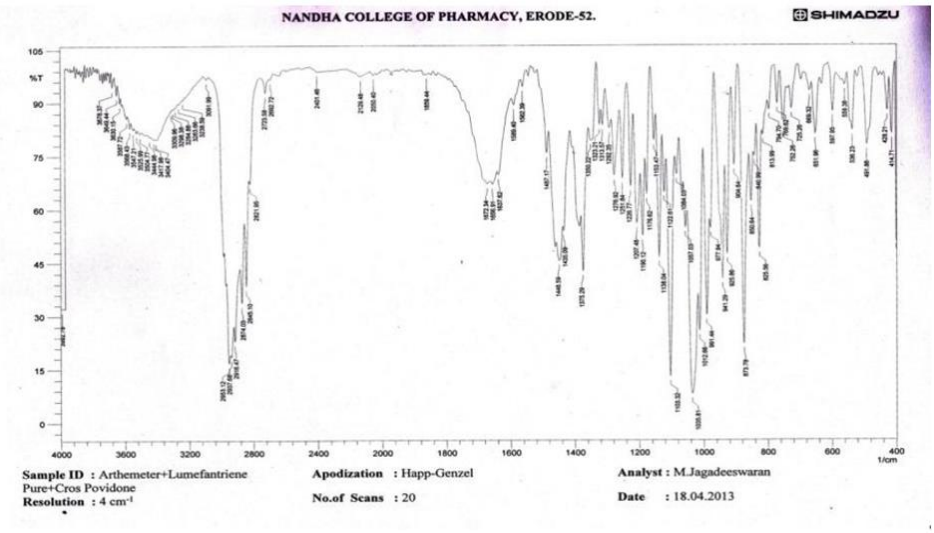

Fig No 5: IR Spectra of Drug (Artemether+Lumefantrine+Crosspovidine)

Table No: 4 Evaluation of Blend

Batchcode	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose	Carr'sindex	HausnerRatio
F0	0.62	0.68	$29^0 13$	19.43	1.096
F1	0.55	0.66	$28^0 38'$	16.69	1.131
F2	0.60	0.66	$30^0 38'$	16.66	1.141
F3	0.60	0.74	$29^0 79'$	19.43	1.233
F4	0.58	0.66	$30^0 38'$	16.66	1.137
F5	0.56	0.64	$28^0 79'$	15.55	1.107
F6	0.56	0.65	$27^0 23'$	13.84	1.160

CONCLUSION

As per flow ability scale, the drug has good characteristics to flow. The excipients did not make any effect on the flow of blend. Thus it was decided to use direct compression method.

Evaluation of Physical Parameters of the FDT Formulations

Table No: 5 Evaluation Parameters of Batch F0 to F6

Parameters	F0	F1	F2	F3	F4	F5	F6
Weight variation (mg)	408.48	406	404.80	405.6	407	406.40	408
Thickness(mm)	3.50±0.055	3.5±0.017	3.53±0.025	3.52 ±0.04	3.52 ±0.04	3.50 ±0.251	3.54 ±0.05
Hardness(kg/cm^2)	3.50±0.04	3.50±0.08	3.50 ±0.03	3.83 ±0.09	3.50 ±0.04	4.00 ±0.05	3.66 ±0.01
Friability(%w/w)	0.40%	0.41%	0.41%	0.51%	0.45%	0.43%	0.39%
Disintegration time (sec)	200 sec	19 sec	16 sec	15 sec	28sec	24sec	19sec
Wetting time(sec)	176±1.527	23	15	12	26	23	19
Assay(%) (artemether)	97.85	98.52	99.67	100.10	99.75	99.63	100
Assay(%) (lumefantrine)	98.65	98.65	99.45	100.50	99.65	99.75	100.10
Water Absorption Ratio(%)	56.45	57.51	59.97	62.87	60.96	61.32	66.45
Invitro dispersion Time(sec)	155±1	18±1	13±0.76	10 ±0.63	19±0.5	15±1	11±0.5

All values mean± S.D

Comparative Study of Disintegration Time of Formulations F1 To F6

Table No: 6 Disintegration time of formulation F1 to F6.

Superdisintegrant	Formulation	Disintegration time (Sec)
Crosspovidine	F1 F2 F3	19 16 15
Sodium starch glycolate	F4 F5 F6	28 24 19

Wetting Time of Formulations:

Table No: 7 Wetting Time of Formulation.

Superdisintegrant	Formulation	Wetting time (sec)
Crosspovidine	F1 F2 F3	23 15 12
Sodium starch glycolate	F4 F5 F6	26 23 19

Dissolution Profile of FDT Formulations

Table No 8: Percentage Cumulative drug release profile of Batch F0 to F6 Artemether

Time (min)	F0	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0
5	5.07	28.47	32.40	33.07	23.07	25.03	30.60
10	9.46	44.97	47.45	50.40	40.40	43.36	45.65
15	15.36	57.27	64.63	70.52	53.83	56.94	63.16
20	21.43	72.81	79.83	86.40	68.89	72.49	78.05
25	26.01	85.25	92.45	99.49	82.14	88.20	91.63

Table. No: 9 Percentage Cumulative drug release profile of Batch F0 to F6 Lumefantrine.

Time (min)	F0	F1	F2	F3	F4	F5	F6
0	0	0	0	0	0	0	0

5	4.50	27.93	29.32	30.35	26.53	28.08	29.48
10	9.00	41.74	43.13	45.93	40.03	42.51	44.37
15	14.74	55.55	58.80	60.36	52.91	57.25	58.65
20	19.55	72.15	77.27	79.91	71.22	73.08	78.98
25	24.12	84.10	91.70	99.15	82.39	89.22	92.79

STUDY OF OPTIMIZED FORMULA--TION F-3 USING (CROSSPOVIDINE IN 15%)

It is very essential that any product developed in the formulation department should be stable. The regulatory agencies in different countries try to ensure that the stability studies are carried out on the product. The formulation is subjected to accelerated stability conditions (400C±20C/75% RH ±5%). The effects of temperature and time on the physical and chemical characteristics of the tablet were evaluated for assessing the stability of the formulated tablets. The results indicate that there wasn't any significant change in hardness & % drug content. There is a significant weight gain and increased wetting time. Disintegration and in vitro drug release was found to be increased a little more at 400C temperature. No significant change was observed in drug content.

Accelerated stability studies as per ICH guidelines:

The optimized formulation (F3) was wrapped in aluminum foils and kept in Petri-dish at (400C±20C/75% RH ±5%) in humidity chamber. The stability studies were conducted after15 and 30 days.

Table No 10: Physical Characteristics of Artemether and Lumefantriene Fast dissolving tablet of optimized Batch F3 at Temperature (400C±20C/75% RH ±5%).

Physical parameters	0day	30days	90days
Percentage drug content (%) (arte&lume)	99.49 & 99.15	99.49 & 99.15	99.19 & 98.94
Hardness (kg/cm^2)	3.83	3.83	3.79
Disintegration time(sec)	15sec	15sec	16sec
Wetting time(sec)	12sec	12sec	13sec

Artemether

Table No 11: %Drug release at (400C±20C/75% RH ±5%) 0f optimized Batch F3.

Time (min)	%Drug releasein 0day	%Drug releasein 30days	%Drug releasein 90days
0	0	0	0
5	33.07	33.07	32.62
10	50.40	50.40	49.96
15	70.52	70.52	70.39
20	86.40	86.40	86.24
25	99.49	99.49	99.15

Lumefantrine

Table No 12: %Drug release at (400C±20C/75% RH ±5%) 0f optimized Batch F3.

Time (min)	%Drug releasein 0day	%Drug releasein 15 days	% Drug release in 30 days
0	0	0	0
5	30.25	30.25	30.13
10	45.93	45.93	45.76
15	60.36	60.36	60.19
20	79.91	79.91	77.34
25	99.15	99.15	98.94

SUMMARY AND CONCLUSION

Artemether and lumefantrine are artimisinin combination therapies (ACT) that are widely used in the treatment of acute uncomplicated resistant falciparum malaria by combining one of the artemisinin compounds with another effective erytocytic schizontocide. The notion of preparing orally disintegrating tablets of arteme ther and lumefantrine provides an appropriate and practical strategy to achieving the desired goal of quicker disintegration and dissolution with increased bioavailability. As a result, in order to improve patient compliance in treatment, a novel drug delivery strategy for artemether and lumefantrine, namely orally disintegrating tablets, must be developed. The current study aims to reduce disintegration time and improve medication release with a quicker beginning of action.

Conventional artemether and lume fantrine tablets are not suited for use when a rapid onset of action is required. To address these issues, there is a need to design a quickly dissolving dosage form, preferably

one that may be delivered without water anywhere and at any time. There is no such thing as a quick dissolving tablet of artemether and lumefantrine.

The drug excipients compatibility investigations were performed using FT-IR analysis, which revealed that there was an interaction between the drug and the excipients selected for the formulation.

Weight fluctuation, Friability, hardness, and Assay findings for all formulations were determined to be within the normal pharmacopoeial limit. Overall, the formulation F3 containing 15% w/w crosspovidine was found to be promising, with an in vitro dispersion time of 10 sec, disintegration time of 15 sec, wetting time of 12 sec, and water absorption ratio of 62.83% when compared to the control formulation (F0), which has values for the above parameters of 155sec, 200 sec, 176 s, and 56.45%. The experimental data also demonstrates that crospovidine produces equivalent, if not somewhat better, outcomes than ssg. In addition, as compared to a commercial standard tablet of crosspovidine, Formulation F3 exhibits quicker drug release.

The stability investigations were carried out in accordance with I.C.H requirements. The content uniformity, in-vitro disintegration time, wetting time, hardness test, and in-vitro drug release study of Formulation F3 were all considered. The formulation had no significant fluctuations in any of the parameters and was stable for 90 days.

The tablets made were determined to be satisfactory, without chipping and sicking with ideal hardness and thickness. The tablets made with a 15% crosspovidine ratio were observed to dissolve quickly, had rapid drug release in a short period of time, and to be stable. By raising the concentration of superdisintegrants, the rate of medication release is raised and disintegration time is shortened significantly. When a result, as the concentration of super disintegrant increases, so does the rate of drug release and disintegration time. This study shows that using a direct compression approach with a mixture of superdisintegrants may greatly improve the disintegration of artemether and lumefantrine.

REFFERENCES

1. R. Margret Chandira, B.Jaykar & Debjit Bhowmic, “Fast dissolving tablets: An overview”, has been published in Journal of chemical

and pharmaceutical research, 2009, 1 (1) : 163 – 177.

2. Leon lachman, A.Lieberman and joseph.L.Kaing The theory and practice of industrial pharmacy 3rded. Bombay: Vaerghese publishing house; 1986
3. Brahmankar D. M. and Jaiswal S.B., in, “Biopharmaceutics and Pharmacokinetics”, "A Treatise”, 1st edn, 1995, Vallabh Prakashan, 347-371.
4. Lachman Leon, Liberman H.A.and Kanig J.L., “The Theory and Practice of Industrial pharmacy”, 3rd edn, Varghese publishing House, Bombay, 346-372.
5. Palanisamy. P, R. Margret Chandira, B. Jaykar, A.Pasupathi, B. S. Venkateshwarlu, M. Kumar, M. V. Kumudhavalli, “Formulation and evaluation of inlay tablet of metformin hydrochloride as sustained release and pioglita zone with glibenclamide as immediate release” , Journal of Pharmacy Research, 2014,8(11),Page. No: 1592-1607.
6. Palanisamy. P and B.Jaykar “Formulation and evaluation of controlled release mucoadhesive matrix tablet of nadolol”, world journal of pharmaceutical research, 2015, Volume 4, Issue 8, 1223-1232.
7. R. Margret Chandira, P. Palanisamy, B.Jayakar “Design And Development Of Controlled Release Mucoadhesive Oral Tablet Of Clarithromycin”, International Journal of Pharma Recent Research, 2009, 1(1), Page. No: 59-66.
8. R. Margret Chandira, P. Palanisamy, B. Jayakar “Formulation and Evaluation of Effervescent Tablets of Aceclofenac”, International Research Journal of Pharmacy, December--2011; Volume.no:2, Issue (12), Page. no: 185-190.
9. Palanisamy. P and B.Jaykar “Formulation and evaluation of controlled release mucoadhesive matrix tablet of nadolol”, world journal of pharmaceutical research, 2015, Volume 4, Issue 8, 1223-1232.
10. Ahlneck, C., and Zografi. 1990. The molecular Basis of moisture effects on the physical and chemical stability of drugs in the solid state, Int. J. Pharm. 62: 87-85.
11. ICH Guideline Published by Europian Medicines agency CAMP /ICH/ 2736/99 August 2003