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FORMULATION AND EVALUATION OF IMMEDIATE RELEASE PELLETS CONTAINING ARTEMETHER AND LUMEFANTRINE

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Abstract

The present study was aimed to develop a novel immediate releasing drug delivery system for anti malarial drugs. The immediate release pellets loaded with solid dispersed pellets are useful in increasing the Acceptability & Palatability of children due to small size of the pellets and increased solubility of the drug. Artemether and Lumefantrine are used to treat uncomplicated malaria caused by *P. falciparum* in a fixed ratio dosage of (1:6). The main aim of the present study was to develop solid dispersed immediate release pellet to increase the patient compliance. The solid dispersed immediate release pellets were prepared by Extrusion and spheronization method using two super disintegrates in 4%, 6%, 8% percentages of Crospovidone and Croscarmellose sodium. The solid dispersed immediate release pellets were evaluated for compatibility, crystalline nature of the drug, uniformity of drug, friability, pellet size and *in vitro* dissolution studies. FTIR results indicated that there was no incompatibility between the drug and the polymers. The optimized formulation of Artemether (SDAF5) has lowest friability (0.72±0.18), pellet size (1.32±0.12). *In vitro* dissolution study showed that the drug release was found to be 94.55±0.58 % at the end of 60mins in 900 ml of P^H 7.2 Phosphate buffer and 0.5%SLS at 37±0.5 °C. In case of Lumefantrine, The optimized formulation of Lumefantrine (SDRF5) has lowest friability (0.65±0.32), pellet size (1.29±0.45). *In vitro* dissolution study showed that the drug release was found to be 94.19±0.98 % at the end of 120mins in 900 ml of P^H 1.2, 0.1N HCl and 0.5%Tween 80 at 37±0.5 °C. The study demonstrated that Solid dispersed immediate release pellets containing 6% of Croscarmellose sodium could be successfully formulated.

Keywords: Immediate Release Pellets, Artemether, Lumefantrine, Solid Dispersion, Pellets.

Introduction

Malaria has been described since ancient times as a seasonal periodic fever. The name malaria is originated from Latin's *mal aira* which means bad air. The symptoms shown by malaria are fever, headache, muscle ache, back pain, joint pains, chest pain, nausea, sometimes vomiting, cough, in severe cases it leads to coma and finally it causes death approximately one million people every year [(1)]. Artemether and Lumefantrine are used to treat uncomplicated malaria caused by *P. falciparum* in a fixed ratio dosage of (1:6).

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Among all drug delivery systems, oral delivery is the most convenient and commonly employed route of drug delivery because it possesses many advantages compare to other routes of drug delivery systems. Easy administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design are the major advantages of this dosage form[(2)]. The poor oral bioavailability of the drug is due low solubility, low dissolution of the drug rather than permeation of the drug through epithelia of gastro intestinal tract. Hence permeability, solubility and dissolution of a drug play an important role in determining the bioavailability of a drug when administered orally. In order to increase bioavailability, solubility of a drug should be increased. There are various techniques to increase solubility of a drug[(3)]. Among them solid dispersion (solvent evaporation method, fusion process, melt-mixing, freeze-dried, fusion-solvent method, kneading technique, co- precipitation) is commonly used technique used to increase the solubility of a drug.

The concept of solid dispersions was originally proposed by Sekiguchi and Obi, in 1961. They developed practical method and achieved success in improving the solubility of poorly water drugs by using the hydrophilic carrier[(4)]. The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug.

Artemether and Lumefantrine are highly lipophilic drugs and are poorly soluble in water with bioavailability of 1.18ug/ml and 0.44ug/ml respectively. Artemether is it has rapid onset of action and 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[(5)].As both the drugs belongs to BCS class IV having low solubility and low permeation[(6,7)]. The solubility of a drug is increased by solid dispersion(solvent evaporation) technique.

Even after increasing the solubility of the drug, Acceptability & Palatability of pediatric dosage forms is the one of the major problem which is encountered during formulations especially in case of bitter drugs used for pediatric formulations. Palatability is defined as the property of being acceptable to the mouth ‘TASTE’ and acceptability to the mind or feelings acceptability. Generally Acceptable size of tables is 3-5mm > 2yrs, 5-10mm>6yrs, 10-15mm>12yrs and15mm+>18 yrs. According to the survey conducted by American Society of Pediatric: 2000, 91% of unacceptance of the drug is due to the unpleasant taste and size of the formulation. So in order to increase the Acceptability & Palatability of drugs by children many attempt has been made, one among them is by using novel delivery system called Multi particulate drug delivery system (pellet).

Pellets are small, free flowing, systematically produced, spherical or semi spherical solid units, geometrically defined agglomerates of about size ranging from 0.2 mm to 2.0 mm, obtained from diverse starting materials of fine powders or granules of bulk drugs and excipients utilizing different pelletization techniques[(8)]. Pellets have many advantages they Disperse freely in the GI& invariably maximize drug absorption, Reduce peak plasma fluctuation, Minimize potential side effects without lowering bioavailability Avoiding high local concentration, Taste masking of the drug can also be done very easily[(9,10)]. The recent novel trends of pellets are used in formulating modified release multiple dosage form with different release patterns like immediate and sustained release pattern, in taste masking of the drugs which are bitter in taste, available as mouth melt pellets, as polymer based pellets for control release pattern of drug, as fast dissolving tablets containing micro pellets, As a self emulsifying pellets, Gastro retentive floating pellets etc. This trend of pellets has increased patient acceptance.

In the present study an attempts has made to Increase the Acceptability & Palatability of solid dispersed Artemether and Lumefantrine pellets prepared by Extrusion and spheronization method. An attempt has made to mask the taste of the drug to some extent using various taste masking agents[(11)] and also tried to study the effect of various concentration of two super disintegrates[(12)] on releasing pattern of the drug from the dosage form.

Materials

Solid dispersed Artemether, Solid dispersed Lumefantrine, Microcrystalline cellulose, Croscarmellose sodium, Crospovidone, Aspartame, Citric acid, Lactose, Mannitol, Orange flavor. All solvents and chemicals were used of analytical grade.

Methods

IR pellet preparation

Preparation of Solid dispersed pellets of Artemether [13]

Solid dispersions of Artemether in PVP K-30 and PEG 6000 in the ratio of 1:3:2, previously reported as the optimized solid dispersion, was used as the starting material for preparation of pellets .130mg of SD equivalent to 20mg of the drug was taken and different trail formulations (SDAF1-SDAF5) were prepared using two different super disintegrates in different ratios and other excipients. The composition chart of all formulations is given in the Table 1.

Pellets were prepared by extrusion and spheronization method. Prior to pelletization all the solid dispersion, fillers, super disintegrates and other excipients were blended in a double cone blender (VJ instruments) for uniform mixing, blending is done for 10 min .After 10min pass all the ingredients through sieve no.40 then added required amount of distilled water to bind the mass to obtain a dove mass which was extruded using sieve no. 10. The extrudates were immediately spheronized. Thus obtained pellets were dried at 40 ºC for 2hrs in the hot air oven (Bio technics India, Model Bio =26) or air dried for overnight.

Preparation of Solid dispersed pellets of Lumefantrine

In case of Lumefantrine all the preparation process of solid dispersed Artemether pellets were kept same except the amount of solid dispersion which was previously reported as optimized solid dispersion being used was 730mg of SD equivalent to 120mg of the drug was used as a starting material for the preparation of solid dispersed pellets of Lumefantrine. The composition chart of all formulations is given in the Table 1. Thus obtained dried pellets of Artemether, Lumefantrine are mixed in the ratio of 1:6 fixed ratios and stored in a container.

Formulation chart for Artemether and Lumefantrine

Table No. 01: Composition of various Solid Dispersions of Artemether

Ingredients	SDA5F1	SDA5F2	SDA5F3	SDA5F4	SDA5F5	SDA5F6
Solid dispersed Artemether (mg)	130	130	130	130	130	130
Microcrystalline Cellulose (mg)	63	58	53	63	58	53
Crospovidone (mg)	10	15	20	-	-	-
Croscarmellose Sodium (mg)	-	-	-	10	15	20
Spray dried Lactose (mg)	30	30	30	30	30	30
Mannitol (mg)	10	10	10	10	10	10
Citric acid (mg)	3	3	3	3	3	3
Aspartame (mg)	4	4	4	4	4	4
Water	q.s	q.s	q.s	q.s	q.s	q.s

Table No. 02: Composition of various Solid Dispersions of Lumefantrine

Ingredients	SDR5F1	SDR5F2	SDR5F3	SDR5F4	SDR5F5	SDR5F6
Solid dispersion drug (mg)	730	730	730	730	730	730
Microcrystalline Cellulose(mg)	81	63	45	81	63	45
Crospovidone (mg)	36	54	72	-	-	-
Croscarmellose Sodium (mg)	-	-	-	36	54	72
Lactose (mg)	30	30	30	30	30	30
Mannitol (mg)	12	12	12	12	12	12
Citric acid (mg)	3	3	3	3	3	3
Aspartame (mg)	8	8	8	8	8	8
Water	q.s	q.s	q.s	q.s	q.s	q.s

Evaluation parameters for solid dispersed immediate release pellets

FT-IR studies[14]

FTIR was performed for pure drug, blank (only Excipient without drug) and optimized Solid dispersion were obtained on FTIR (Perkin Elmer spectrum one, UK) Spectrophotometer. Samples (About 3 mg of sample and 100 mg of potassium bromide) were mixed, compressed into pellets and transmittance was measured from wave number 450 to 4000 cm^{-1} using FT-IR spectrophotometer (FTIR –T2154, Perkin Elmer, UK)

Friability [15]

The friability test was performed on the pellets to ensure their mechanical strength. Lower friability values indicate good mechanical strength. Pellets of known mass (500mg) were placed in a Roche Friability tester (DBK Friability tester) and subjected to impact testing at 25 RPM for 4 min.

$$\text{Friability (\%)} = 1 - \frac{[\text{initial weight}]}{[\text{Weight retained}]} \times 100$$

Drug content Estimation [16]

Accurately weighed 100mg of Solid dispersed pellets of Artemether were dissolved in 100ml of P^H 7.2 phosphate buffer containing 0.5% SLS phosphate buffer and sonicated it for 5min. Suitably diluted and the absorbance was measured at λ_{max} 211 nm using an UV spectrometer (UV-1800 Shimadzu corporation, Japan). In case of Lumefantrine all the process kept same except the buffer being used is P^H 1.2 buffer, 0.1N HCl containing 0.5%Tween80 was used, the absorbance was measured at λ_{max} 342 nm using an UV spectrometer (UV-1800 Shimadzu corporation, Japan). The limit for drug content estimation is 85-115%. The drug content was determined by the formula.

$$Drug Content = \frac{Concentration\ X\ Dilution\ factor\ X\ Dissolution\ medium}{1000}$$

Pellet Size Analysis [17]

The pellet size of drug loaded formulations was measured by an optical microscope fitted with an ocular and stage micrometer and particle size distribution was calculated. The Olympus model (SZX-12) having resolution of 40x was used for this purpose. The instrument was calibrated at 1 unit of eyepiece micrometer was equal to 1/30mm (33.33µm).

***In Vitro* Dissolution Studies** [18,19]

In vitro dissolution studies of solid dispersed Artemether pellets was carried out using USP type II dissolution testing apparatus (paddle type, TDL-08L, Electrolab, Mumbai, India) in 900ml of P^H 7.2 Phosphate buffer maintained at 37±0.5°C stirred at 50 rpm.0.5% SLS was used to create sink condition. In case of Lumefantrine all the parameters were kept same except the dissolution medium being used was P^H 1.2, 0.1N HCl and Tween 80 was used to create sink condition. An aliquot of 5ml Samples were withdrawn at specific time intervals, replacing the same amount with the fresh medium in order to keep the total volume constant. The samples were analyzed using spectrophotometrically (UV-1800 Shimadzu) at a λ_{max} of 211nm for Artemether and 342 nm for Lumefantrine after suitable dilutions.

Results and discussion

FTIR Studies

FTIR studies were carried out for the pure drug – Artemether, formulation SDAF5 and their spectra are as shown in Fig. 1 & Fig. 2 respectively.

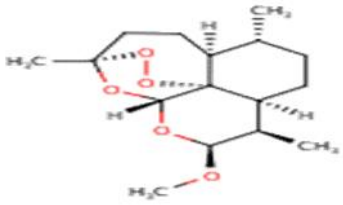

Fig. No. 03: Structure of Artemether

The characteristic peaks of the pure drug – Artemether was assigned from standard literature. These included O-H stretching, C-H stretching, C-H bending and are as shown below.

1. 3462.34 cm^{-1} : O-H stretching
2. 2937.48 cm^{-1} : C-H stretching
3. 1433.51 cm^{-1} : C-H bending

As seen in Fig. 2, the spectra for Artemether exhibits a broad peak at **3462.34 cm^{-1}** due to alcohols and phenols (O-H) stretching vibration, **2956.97 cm^{-1}** due to alkanes (C-H) stretching vibration, **1433.51 cm^{-1}** due to alkanes (C-H) bending vibration.

The FTIR results from optimized formulation SDAF5 exhibited broad peaks at **3346.61 cm^{-1}** due to alcohols and phenols (O-H). **2933.83 cm^{-1}** due to alkanes (C-H) stretching vibration, **1433.51cm^{-1}**

due to alkanes (C-H) bending vibration.The intensity and position of these characteristic peaks permits easy interpretation of any possible interaction between the drug and the excipients in the formulation. The results clearly showed that there was no interaction between the drug and the excipients in the prepared formulation SDAF5. The drug - Artemether was intact and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into pellets. FTIR studies were carried out for the pure drug – Lumefantrine, formulation SDAR5 and their spectra are as shown in Fig. 4 & Fig. 5 respectively.

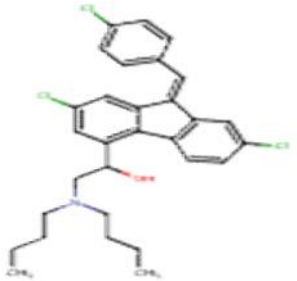

Fig. No. 06: Structure of Lumefantrine

The characteristic peaks of the pure drug – Artemether was assigned from standard literature. These included O-H stretching, C-H stretching, C-H bending and are as shown below.

1. 3394.72 cm^{-1} : O-H stretching
2. 2951.82 cm^{-1} : C-H stretching
3. 1442.13 cm^{-1} : C-H bending

As seen in Fig. 2, the spectra for Artemether exhibits a broad peak at **3394.72 cm^{-1}** due to alcohols and phenols (O-H) stretching vibration, **2951.82 cm^{-1}** due to alkanes (C-H) stretching vibration, **1442.13 cm^{-1}** due to alkanes (C-H) bending vibration. The FTIR results from optimized formulation SDRF5 exhibited broad peaks at **3385.18 cm^{-1}** due to alcohols and phenols (O-H). **2945.40 cm^{-1}** due to alkanes (C-H)stretching vibration, **1437.02---- cm^{-1}** due to alkanes (C-H) bending vibration. The results clearly showed that there was no interaction between the drug and the excipients in the prepared formulation SDRF5. The drug – Lumefantrine was intact and there was no sign of any degradation due to preparative processes adopted during the loading of the drug into pellets.

Drug content

The drug content estimation was done to ensure uniform distribution of drug. The drug content of Artemether was performed for all the prepared formulations and tabulated in Table 3. Obtained results indicates that in the all the formulations drug content was uniform and ranged between 90 .00% to 97.90 % which was analyzed spectrophotometrically at λ_{max} 211nm. All the formulations showed the presence of high drug content. Among all formulations SDAF5 formulation has maximum amount of drug (97.90%).

In case of Lumefantrine the drug content was analyzed spectrophotometrically at λ_{max} 342 nm and the drug content from all formulation was found to be in between 98.20 % to 98.95 %. Among all formulations SDRF5 formulation has maximum amount of drug (98.95%). Results are shown in Table 4. This results indicates that the drug was uniformly distributed in all formulations and all the formulations are within the specified limits of 85-115%.

Friability

Friability is measure to assess the mechanical strength of the pellets in terms of fragmentation or powder during handling and transit. Friability of the pellet formulations was in the range 0.65% to 0.98%, the optimized formulation SDAF5 has 0.72% of Friability. In case of Lumefantrine Friability of the pellet formulations was in the range 0.55% to 0.99%, the optimized formulation SDRF5 has 0.65% of Friability. From the above results, it indicates that the friability of pellets lies in the expected range less than 1% as per FDA specifications.

Pellet size analysis

The pellet size of the drug loaded formulations was measured by optical microscope for formulations (SDAF1-SDAF6). The size of pellets from all formulations ranges between 1.28mm-1.33mm. The optimized size of pellet for an optimized formulation (SDAF5) is 1.32mm. Results were shown in Table 3. In case of Lumefantrine size of pellets from all formulations (SDRF1-SDRF2) ranges in between 1.26mm-1.31mm. The optimized size of pellet for an optimized formulation (SDRF5) is 1.29mm. Results were shown in Table 4.

***In Vitro* Dissolution Studies**

In vitro dissolution studies of Artemether from solid dispersed pellet formulations containing Artemether: PVP K-30: PEG 6000(1:3:2) were carried in the P^H 7.2 Phosphate buffer and 0.5% SLS. The results obtained from the dissolution study reveals that the percentages of drug release at the end of 60^{th} minute was in between 82.32% to 94.55% for formulations SDAF1 to SDAF5. The dissolution profiles of all the formulations are depicted in Fig. 7. Optimized formulation SDAF5, containing 6% of Croscarmellose sodium released 94.55% drug at the end of 60^{th} minute. The immediate release of the drug from pellets is due to presence of Croscarmellose sodium in the pellet and hydrophilic polymers (PEG 6000 and PVP K-30) in the solid dispersion.

When 6% Croscarmellose sodium containing pellet exposed to dissolution medium, Croscarmellose sodium rapidly swells to 4-8 times its original volume and facilitates rapid absorption of medium followed by disintegration and dissolution of the drug. The hydrophilic polymers of the solid dispersion promotes wetting, dispersibility and gives porous nature to the formulation this facilitates faster dissolution rate. Due the combined effects of Croscarmellose sodium, PEG 6000 and PVP K-30 may be the reason for rapid dissolution of immediate release pellets.

The data obtained from comparative *In vitro* dissolution studies between was Pure Artemether, solid dispersion (SDA5) and optimized pellet formulation (SDAF5) reveals that the percentage of drug release from the pure Artemether, optimized solid dispersion(SDA5) and optimized pellet formulation (SDAF5) at the end of 60^{th} minute are 24.21%, 97.80% and 94.19 % respectively. The dissolution profiles of all the formulations are depicted in Fig. 8.

In case of Lumefantrine *In vitro* dissolution studies of Lumefantrine from solid dispersed pellet formulations containing Artemether: PVP K-30: PEG 6000(1:3:2) were carried in the P^H 1.2, 0.1N HCl and 0.5%Tween 80 . The results obtained from the dissolution study reveals that the percentages of drug release at the end of 120 minutes was in between 30.17% to 94.55% for formulations SDRF1 to SDRF5. The dissolution profiles of all the formulations are depicted in Fig. 9. Optimized formulation SDRF5, containing 6% of Croscarmellose sodium released 94.55% drug at the end of 120 minutes .Remaining study kept same as Artemether.

The data obtained from comparative *In vitro* dissolution studies between was Pure Lumefantrine, solid dispersion (SDR5) and optimized pellet formulation (SDRF5) reveals that the percentage of drug release from the pure Lumefantrine, optimized solid dispersion (SDR5) and optimized pellet formulation (SDRF5) at the end of 120 minutes are 16.95 %, 94.55% and 96.67% % respectively. The dissolution profiles of all the formulations are depicted in Fig. 10.

The time taken to release the drug from the pellet formulation is more compare to powdered solid dispersion. This might be due to the compactness of the pellets caused by the extrusion and spheronization of the formulation in the presence of the sphere forming agent (Microcrystalline) and the binder liquid (water).

The order of drug release is solid dispersion> optimized formulation>pure drug.

Table No. 03: Evaluation of Solid dispersed immediate release pellets of Artemether.

Formulation code	Drug content estimation (%)*	Friability (%)*	Pellet size (mm)*	%CDR at 60 mins*
SDAF1	90.00±0.58	0.98±0.74	1.30±0.56	82.32±2.01
SDAF2	96.10±0.19	0.76±0.45	1.27±0.19	84.14±1.82
SDAF3	97.90±0.56	0.65±0.25	1.29±0.44	89.74±1.75
SDAF4	92.61±0.92	0.90±0.45	1.33±0.34	86.31±2.01
SDAF5	97.90±0.16	0.72±0.18	1.32±0.12	94.55±1.58
SDAF6	95.05±0.81	0.65±0.28	1.29±0.98	92.69±1.98

*Mean ±SD, n=3

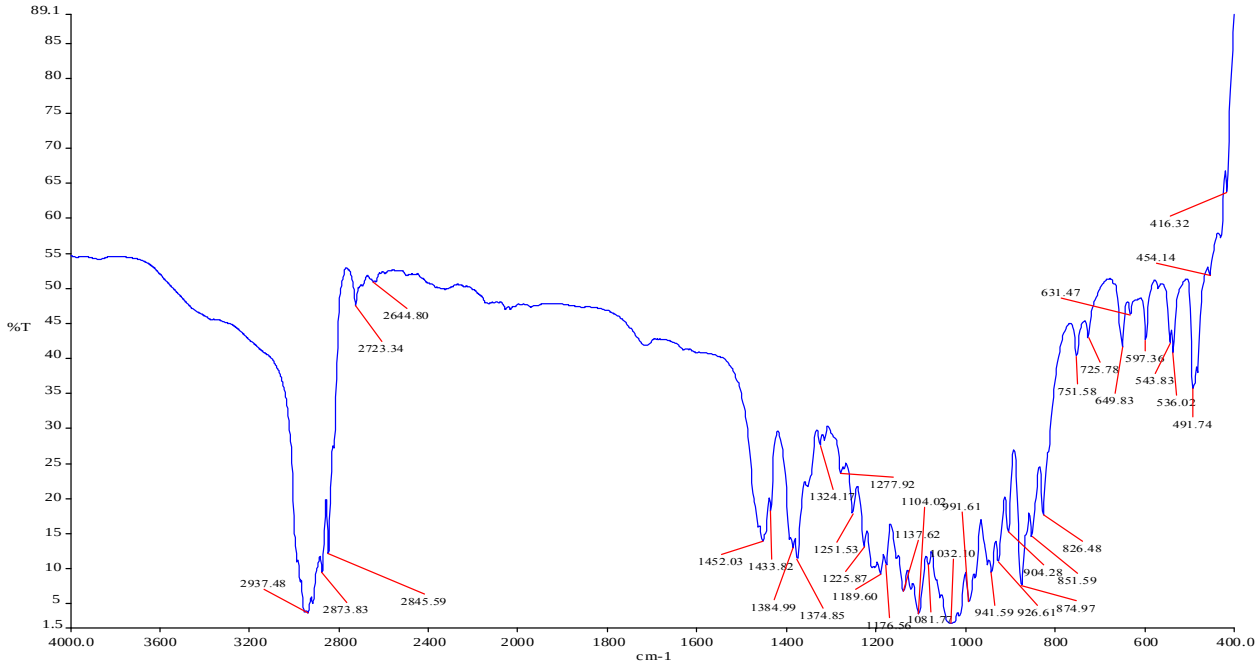

Fig. No. 01: FTIR Spectra of pure drug Artemether

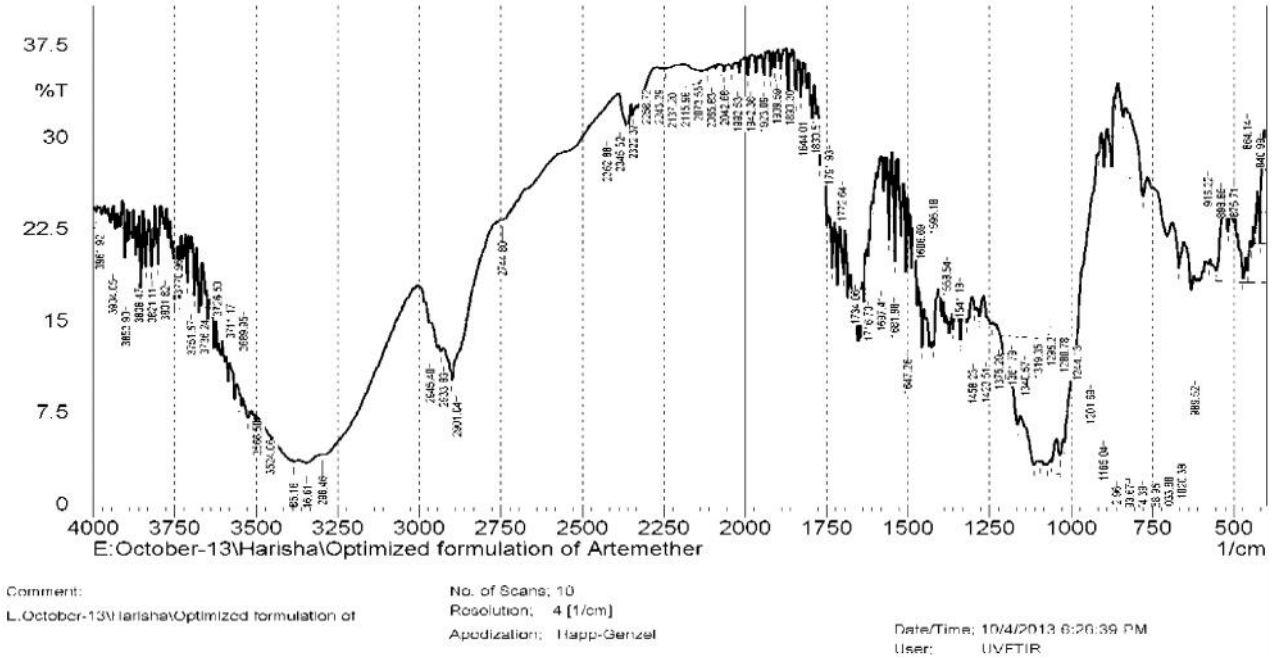

Fig. No. 02: FTIR Spectra of Optimized Formulation SDAF5

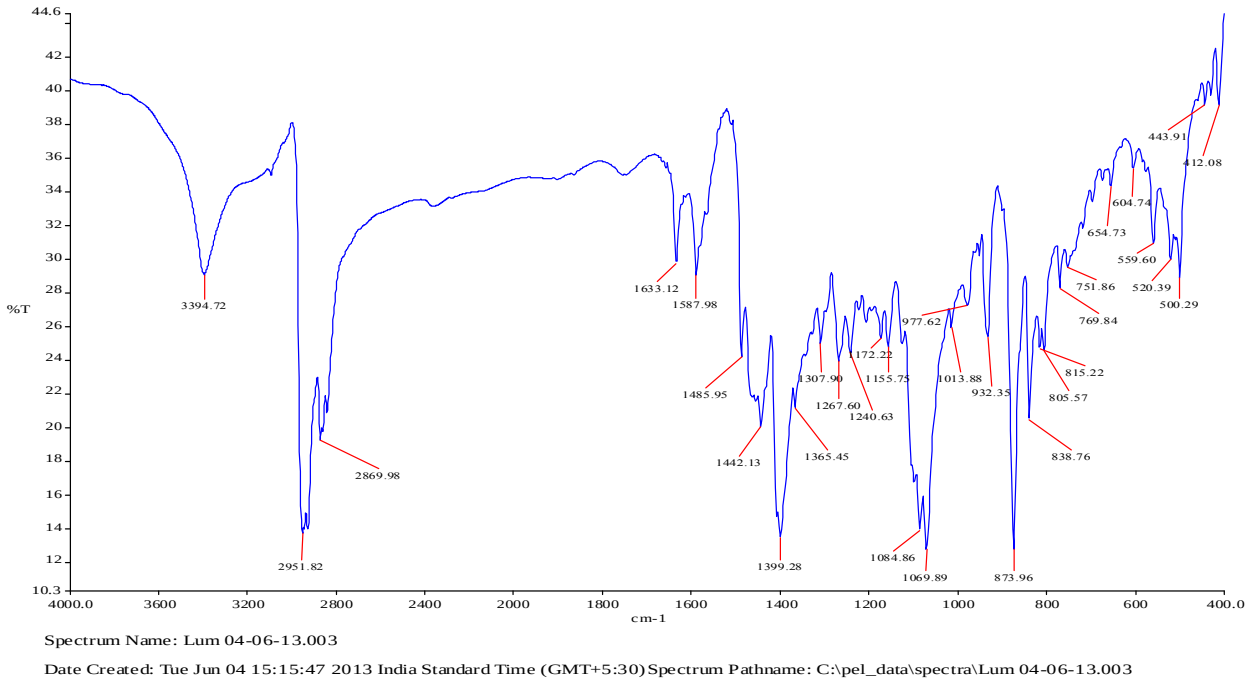

Fig. No. 04: FTIR Spectra of pure drug Lumefantrine.

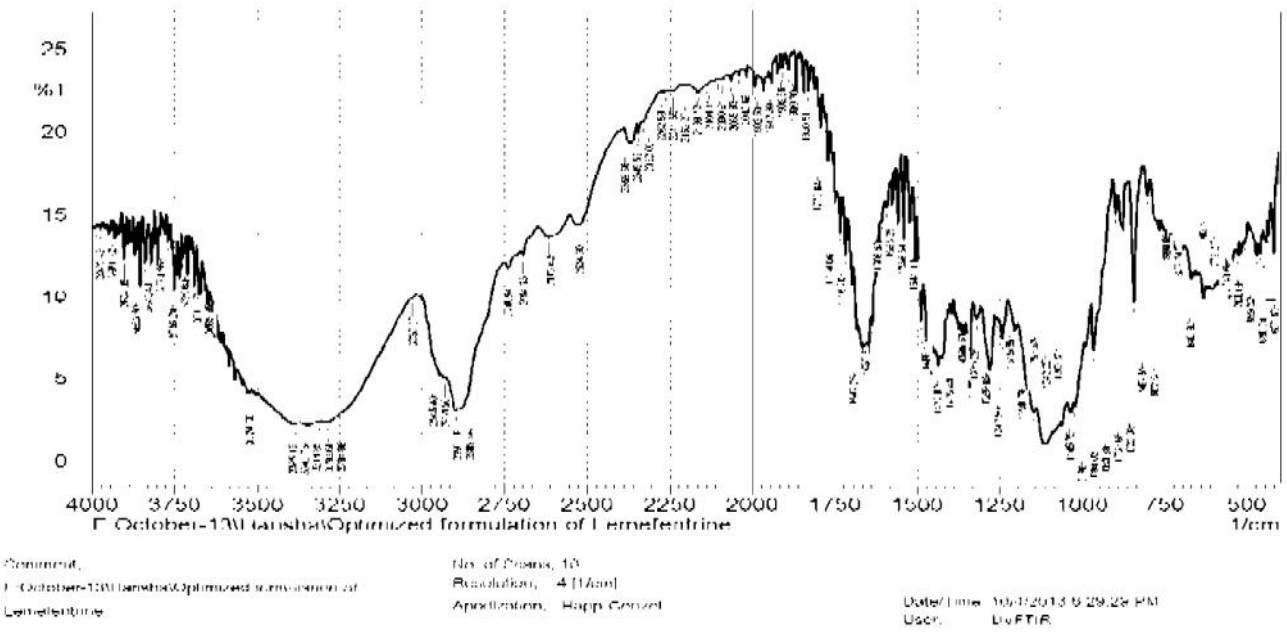

Fig. No. 05: FTIR Spectra of Optimized Formulation SDRF5 of Lumefantrine

Table No. 04: Evaluation of Solid dispersed immediate release pellets of Lumefantrine.

Formulation Code	Drug content Estimation (%)*	Friability (%)*	Pellet size (mm)*	%CDR at 120 mins*
SDRF1	98.90±0.56	0.98±0.29	1.27±1.2	30.17±1.4
SDRF2	98.50±0.89	0.72±0.82	1.30±2.0	79.69±1.8
SDRF3	98.45±0,78	0.58±0.71	1.29±0.92	88.18±1.8
SDRF4	98.20±.76	0.90±0.61	1.31±1.2	46.60±2.2
SDRF5	98.85±0.35	0.65±0.32	1.29±0.45	94.19±0.98
SDRF6	98.76±0.41	0.55±0.54	1.26±0.98	93.15±1.2

*Mean ±SD, n=3

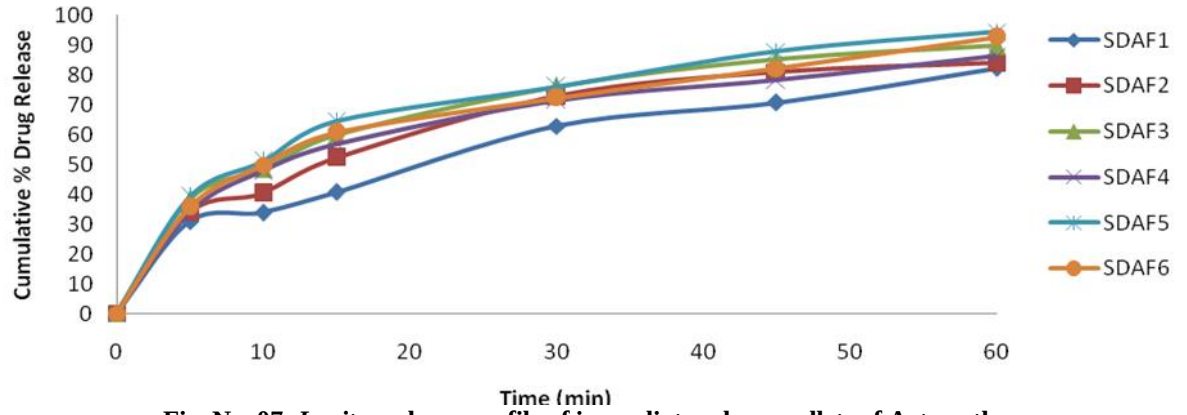

Fig. No. 07: *In vitro* release profile of immediate release pellets of Artemether

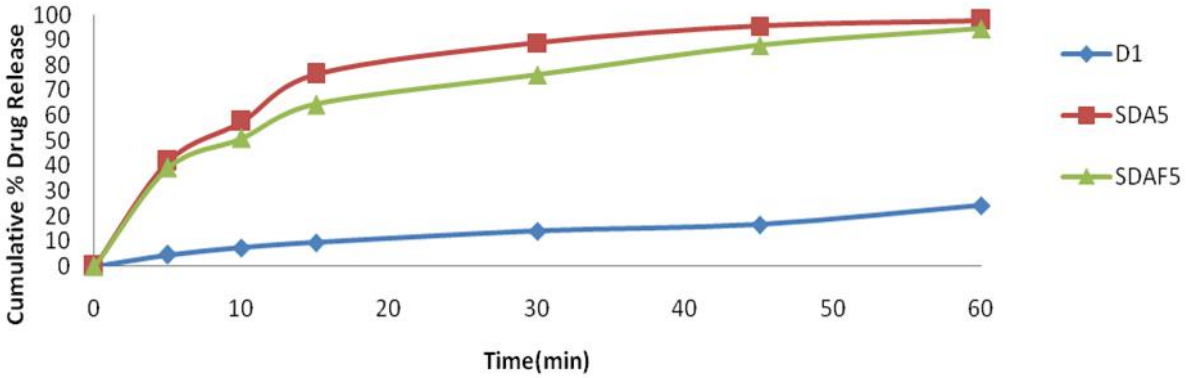

Fig. No. 08: *In vitro* comparative release profile pure drug, solid dispersion, SDAF5 pellet formulation of Artemether.

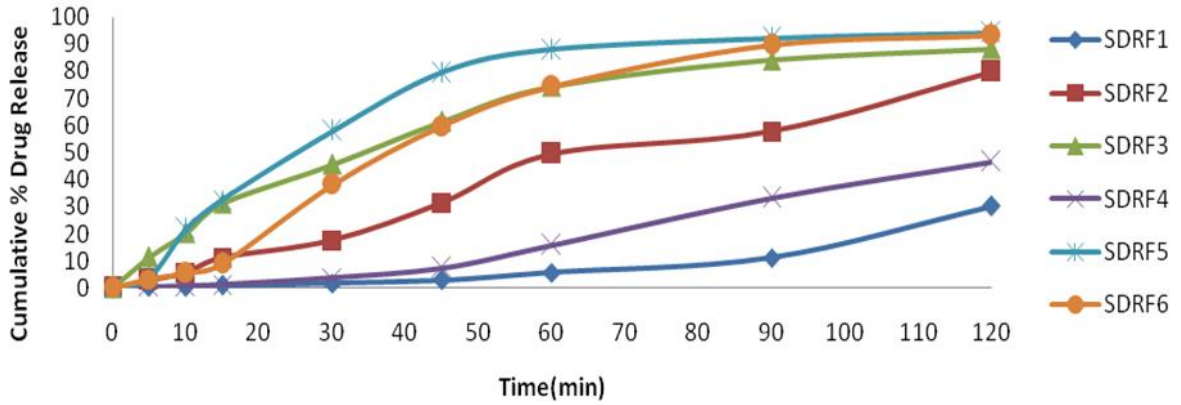

Fig. No. 09: *In vitro* release profile of Lumefantrine from Solid dispersed Pellets

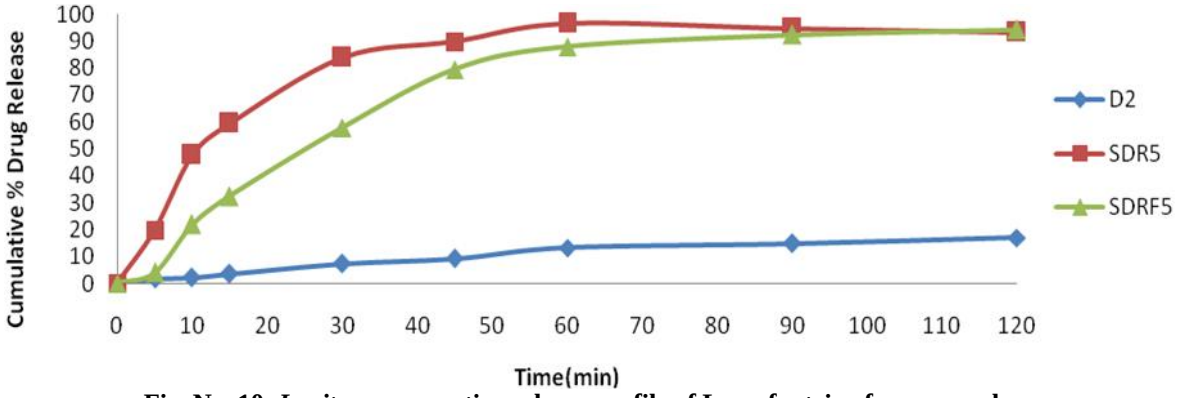

Fig. No. 10: *In vitro* comparative release profile of Lumefantrine from pure drug, solid dispersion, SDRF5 formulation

Conclusion

Solid dispersed immediate release pellets of Artemether and Lumefantrine were prepared by using different ratios of two super disintegrates (Crospovidone and Croscarmellose sodium) by Extrusion and Spheronization method. The immediate release pellets possesses low friability and possessed optimum size. Solid dispersed Artemether and Lumefantrine was successfully incorporated uniformly throughout the pellets. Dissolution studies data reveals due the presence of solid dispersed drug the increased bioavailability of the drug is achieved compare to the pure drug. From the studies it can be concluded that solid dispersed drug along with Croscarmellose sodium of 6% could be successfully formulated into solid dispersed immediate release pellets.

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