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FORMULATION AND EVALUATION OF TABLETS CONTAINING ARTEMETHER MICROSPHERES AND LUMEFANTRINE

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ABSTRACT

This study was aimed to fabricate and evaluate a combination of Artemether and Lumefantrine as tablets and to make Artemether in sustained form so as to prolong its elimination time. Artemether was formulated in form of microspheres by solvent evaporation technique and was then formed into the tablet along with the Lumefantrine. Artemether microspheres were prepared and compressed into compressible tablet by direct compression process using the compressible excipients along with Lumefantrine, and was further evaluated for various parameters such as hardness, thickness, weight variation, friability, drug content, in vitro drug release and stability.

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INTRODUCTION:

Malaria is one of the most important and scourge infectious diseases in developing areas of the world. It is estimated that 300-500 million cases of malaria occur each year resulting in 750,000- 2 million deaths (World malaria situation, 1994). It is transmitted by the bite of female mosquito (Anopheles). Mainly four major species of *Plasmodium* are found in humans (*P.falciparum*, *P.vivax*, *P.ovale* and *P.malariae*)[1]. Effective treatment is dependent on the use of an efficacious anti malarial that is taken according to an optimized regimen. Artemisinin-based combination treatments (ACTs) have the most potent and rapid onset of anti-parasitic activity of any anti-malarial drug available today and are active against all *Plasmodium* species that infect humans[2]. Efficacy is determined by the drug partnering the Artemisinin derivatives and Artemether-Lumefantrine is one such drug combination. The rationale behind this combination is that artemether initially provides rapid symptomatic relief by reducing the number of parasites present before lumefantrine eliminates any residual parasites.

MATERIALS AND METHODS:

Materials

Artemether (ART), Lumefantrine (LUM), Ethyl Cellulose (EC), Polyvinyl alcohol (PVA), Dichloromethane (DCM), Distilled water, Microcrystalline cellulose (MCC), Sodium Starch Glycolate (SSG), Croscarmellose Sodium (CCS), Magnesium Stearate, Colloidal Silicon Dioxide.

Preparation of Artemether Microspheres

Artemether microspheres were obtained by solvent evaporation technique Polymer was dissolved in dichloromethane and then the drug was added to the above solution. This solution was injected into the PVA solution maintained at variable speed using mechanical stirrer. Stirring was continued until all the dichloromethane evaporated. The formed microspheres were collected by filtration andwashed with n-Hexane and dried [3, 4].

Table 1: Formulation codes of Artemether-EC Microspheres

Formulation Codes	Drug (Artemether) (mg)	Polymer (Ethyl Cellulose) (mg)	Solvent (DCM) (ml)	Medium (PVA) (%)	Stirring rate (rpm)
M1	500	1000	20	0.5	200
M2	500	1000	20	0.5	400
M3	500	1000	20	0.5	600
M4	500	1250	20	0.5	200
M5	500	1250	20	0.5	400
M6	500	1250	20	0.5	600
M7	500	1000	20	0.3	200
M8	500	1000	20	0.3	400
M9	500	1000	20	0.3	600
M10	500	1250	20	0.3	200
M11	500	1250	20	0.3	400
M12	500	1250	20	0.3	600
M13	500	1000	20	0.1	200
M14	500	1000	20	0.1	400
M15	500	1000	20	0.1	600
M16	500	1250	20	0.1	200
M17	500	1250	20	0.1	400
M18	500	1250	20	0.1	600

Table 2: Formulation codes of tablets containing ART Microspheres and LUM

FC	ART microsphere	LUM	MCC	SSG	CCS	Mag. Stearate	Colloidal SiO_2
MT1	20	120	107	3	-	7	3
MT2	20	120	105.5	4.5	-	7	3
MT3	20	120	104	6	-	7	3
MT4	20	120	102.5	7.5	-	7	3
MT5	20	120	101	9	-	7	3
MT6	20	120	99.5	10.5	-	7	3
MT7	20	120	98	12	-	7	3
MT8	20	120	96.5	13.5	-	7	3
MT9	20	120	95	15	-	7	3
MT10	20	120	97	-	3	7	3
MT11	20	120	95.5	-	4.5	7	3
MT12	20	120	94	-	6	7	3
MT13	20	120	92.5	-	7.5	7	3
MT14	20	120	91	-	9	7	3
MT15	20	120	89.5	-	10.5	7	3
MT16	20	120	88	-	12	7	3
MT17	20	120	86.5	-	13.5	7	3
MT18	20	120	85	-	15	7	3

Characterization of microspheres

Prepared microsphere should be characterized by following tests such as, Particle size analysis, surface Morphology**,** determination of Percentage yield of microspheres**,** determination of flow properties of microspheres**,** drug entrapment efficiency**,** *In vitro* release studies of microspheres and effect of different formulation variables on various evaluation parameters.

Formulation of Tablets containing microspheres

Tablets of ART microspheres and LUM were prepared by direct compression technique. The corresponding amount of ART microspheres equivalent to 20 mg drug, lumefantrine, MCC and superdisintegrants were accurately weighed and blended. Thereafter the corresponding amount of magnesium stearate and colloidal silicon dioxide were added to the mixture. The mixture was allowed for direct compression into tablets weighing 300mg using a tablet punching machine with 8 mm flat faced punches.

Characterization of tablets

Formulated tablet should be evaluated by following test such as, thickness, diameter, hardness, friability, weight variation, drug content, microscopic evaluation of tableted microspheres and In vitro release of Lumefantrine&Artemether from tablets

RESULTS AND DISCUSSIONS:

Table 3: Evaluation parameters of microspheres

Formulation Codes	Percentage Yield (%)	Entrapment Efficiency (%)	Particle Size (µm)	Cumulative Release (%)
M1	84.87	66.20	18.45	63.03
M2	79.40	60.49	18.30	68.38
M3	94.00	54.06	15.00	71.65
M4	90.28	70.57	23.12	57.85
M5	86.00	67.42	19.10	61.95
M6	70.34	63.23	16.92	69.19
M7	88.33	67.81	21.00	69.01
M8	92.27	61.15	21.00	71.79
M9	91.73	52.81	14.80	76.72
M10	86.68	73.31	22.77	63.38
M11	86.91	69.98	21.87	70.14
M12	66.63	66.98	19.35	74.48
M13	86.00	70.15	26.42	72.51
M14	84.06	68.39	23.80	76.45
M15	76.67	63.86	20.00	84.87
M16	71.88	74.42	26.10	71.02
M17	88.91	71.26	22.45	75.11
M18	90.11	67.07	18.95	79.48

The morphology of the prepared batches of Artemether microspheres was evaluated by Scanning Electron Microscopy (SEM). Scanning Electron micrographs of the microspheres are shown in figure at different magnifications of 70x, 100x and 10000x revealing the spherical and smooth surface.

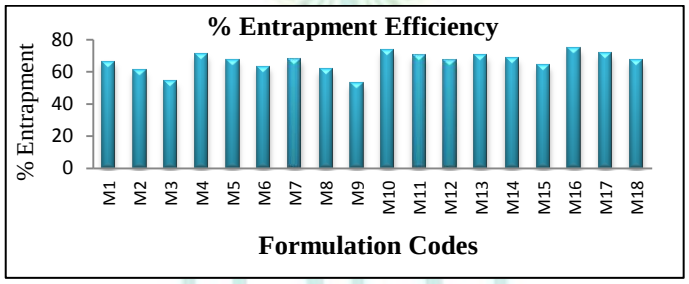

Figure1: Entrapment efficiency (%) of microspheres

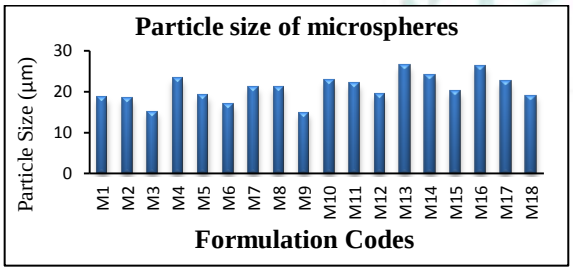

Figure 2: Particle size of microspheres

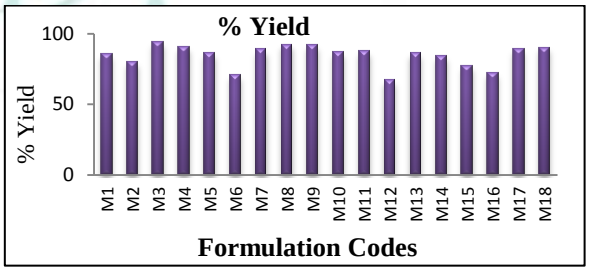

Figure 3: Percentage yield (%) of microspheres

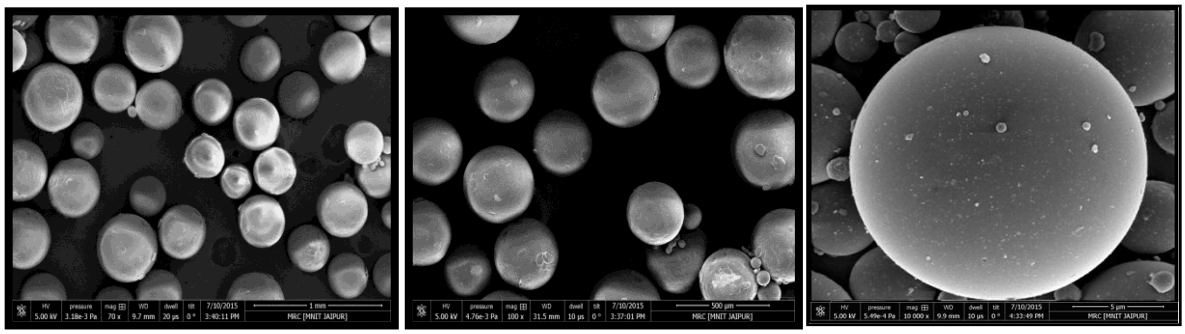

Figure 4: Scanning Electron Micrograph at 70, 100 and 10000 magnification

***In vitro* dissolution studies of art**

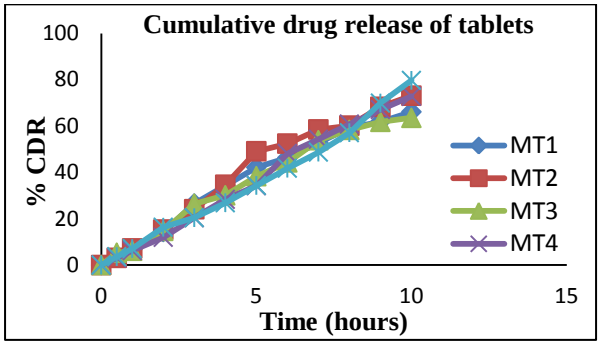

Figure 5: %CDR (ART) of MT1-MT5

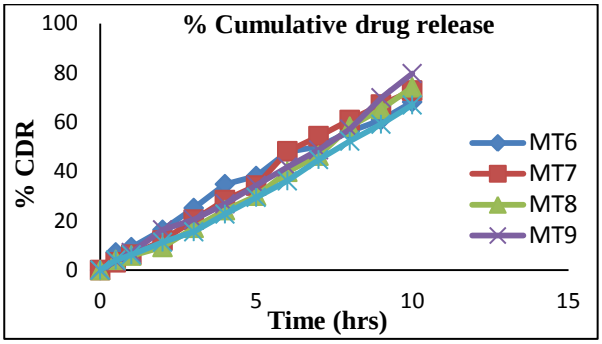

Figure 6: % CDR (ART) of MT6 - MT10

Figure depicts the release rate of ART from the tableted microspheres for all the formulations. At 10th hours release rate of drug was between 61.24% - 86.92%. M15 formulation shows the maximum release and M4 shows the minimum release. It depicts that the release of ART either from microspheres or from the tableted microspheres was found to be relatively near about same. A slight increase is observed in the release from tableted microspheres.

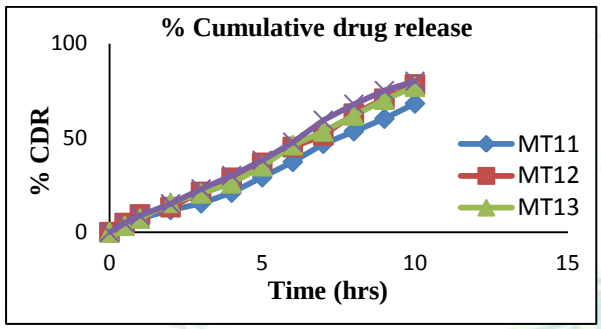

Figure 7: %CDR (ART) of MT11-MT14

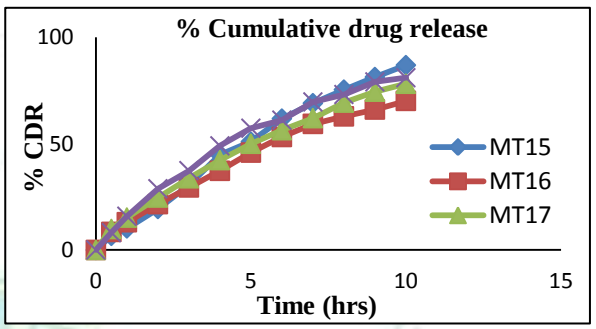

Figure 8: % CDR (ART) of MT15- MT18

CONCLUSION:

Sustained release microspheres of ART were successfully prepared using EC by solvent evaporation technique and after successfully incorporating ART into microspheres, this study aimed to obtain tablets as a final oral dosage form. ART microspheres along with LUM were formulated into tablets by direct compression technique using the excipients. Hence the present work suggest that, ART which has the lower half life and eliminates quickly from the body, when loaded with ethyl cellulose in form of microspheres and tableted along with LUM results in sustained release of drug in malaria. Therefore, ART and LUM in combination minimizes development of resistance as the malaria parasites are never exposed to artemether alone, so are considered as the best combination for treatment of malaria.

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