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Research Article

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A Novel Approach of Artesunate Pellets for the Treatment of Malaria

A. R. Shabaraya*, Ankit S Parulkar, Krishnananda K Kamath, D Shripathy

Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangalore- 574143, Karnataka, India

ABSTRACT

Tropical countries such as India are more prone to the malaria and around 2 million cases are reported annually. Malaria is one of the most prominent life threatening diseases in spite of many efforts made to fight against it. There are many clinically effective anti-malarial agents but the major reasons of malaria treatment failure are due to resistance development, incorrect dosing, poor drug quality, drug interactions, poor drug absorption and misdiagnosis. Current approach done in this study is to formulate a dosage form which can overcome these drawbacks. Here pellets of Artesunate were formulated by extrusion spheronization method using different concentration of ethyl cellulose and evaluated for preformulation studies, drug compatibility studies were carried out. Formulations were evaluated for particles size analysis, zeta potential and *in-vitro* dissolution studies. The pellets were obtained in the size range of 10 – 100µm. The evaluation results obtained showed that the formulation F4 having high concentration of ethyl cellulose showed the best release profile.

Keywords: Malaria, pellets, Artesunate, Extrusion Spheronization, zeta potential.

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***Corresponding author**: Dr. A. R. Shabaraya
Address: Department of Pharmaceutics, Srinivas College of Pharmacy, Valachil, Mangalore- 574143, Karnataka, India
Tel.: +91-9448428200
E-mail ✉: shabaraya1@rediffmail.com
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INTRODUCTION

Recently novel drug delivery systems have showed a remarkable development in the delivering pharmaceutical dosage forms. The novel drug delivery system has a great advantage and fewer side effects over conventional dosage forms. [1] Novel drug delivery system provides a wide variety of formulations such as polymeric pellets, nanocapsules, liposomes, phytosomes, nanoemulsions, microsphere, transferosomes, ethosomes. As compared to conventional dosage forms novel drug delivery systems has a comparatively remarkable advantages over conventional dosage forms such as which include enhancement of solubility, bioavailability, drug targeting, protection from toxicity, enhancement of pharmacological activity, enhancement of stability, improved tissue macrophage distribution, sustained delivery, and protection from physical and chemical degradation. [2-5]

Malaria is one of the most occurring parasitic diseases around the globe causing 1 to 2 million deaths round the world every year and is considered as a life

threatening disease. Chloroquine, amodiaquine, sulphadoxine and pyrimethamine, etc are limited number of clinically effective antimalarial agents but the major problems faced by them are poor bioavailability of the drug and development of resistance against the drug. [6] The artemisinins derivatives artesunate (AS), artemether (ARM), arteether (AE) and dihydroartemisinin (DHA) are the most effective anti-malarial drugs known today. Despite these achievements, Artemisinins and its derivatives have low bioavailability, poor pharmacokinetic properties and high cost. [6-7]

Artesunate is a semi synthetic derivative of Artemesinin which is obtained from a plant product. Artesunate is a prodrug that is rapidly converted to its active form dihydroartemisinin (DHA). It potently inhibits the essential *Plasmodium falciparum* exported protein, a membrane glutathione S-transferase. As a result, the amount of glutathione in the parasite is reduced. Artesunate has a half -life of 0.5 to 1.5 hours. Due to this shorter half -life the use of artesunate becomes very limited. Because of this limitation Artesunate becomes suitable for sustained release formulation. [8]

Pellets are spherical agglomerates of powder particles, prepared by a specialized granulation process, known as pelletization, which was formed by the agglomeration of fine powdered excipient and drugs together that leads to the formation of small free flowing spherical or semi spherical. Pellets possess a uniform shape and size that ranges from 0.5-2.0 mm, about 10% of low porosity and are free-flowing. Pharmaceutically pellets are versatile multiparticulate solid dosage form that can be amenable to both encapsulation into hard gelatin capsules or compression to form tablets and, therefore, may form an excellent carrier system for the controlled oral delivery of both low and high dose drugs. [9] The aim of the project was to prepare sustain release pellets of artesunate for treatment against malaria.

MATERIALS AND METHODS

Gift sample of Artesunate was obtained from Sequent Laboratories Ltd. Mangalore, MCC and Ethylcellulose from Hi media Pvt. ltd Mumbai, Ethanol from Loba chemie Pvt Ltd Mumbai.

Preparation of Artesunate pellets

Pellets were prepared by extrusion/speronization technique. Accurately weighed amount of solid materials with different drug polymer ratios was transferred to a clean bowl and MCC was added (Table 1). The whole mixture was mixed thoroughly. After appropriate mixing the solid masses were passed through sieve no # 40. The mixture was mixed properly by adding ethanol to form a dough mass. The wet mass was extruded through a screen extruder equipped with a standard screen having a 0.8 mm diameter aperture, and rollers rotating at 30 rpm. Spheronization was performed with a rotating plate of regular cross-hatch geometry, at a speed of 800 rpm, for 5 minutes. Pellets were then dried on a tray in a hot oven at 50–60°C for 6 hours. After drying the pellets were kept in dessicator. [10-12]

Table 1: Formula for Formulation of pellets

Ingredients	F1	F2	F3	F4
Artesunate (mg)	50	50	50	50
Microcrystalline Cellulose (mg)	100	100	100	100
Ethyl cellulose (mg)	50	75	100	150

Physicochemical Properties of Drugs

Solubility: Solubility of Artesunate was determined in solvents: water, methanol and chloroform. Excess amount of sample were added in 10 ml of solvent with stirring (300 rpm), at temperature 25 ± 0.5°C for 48 h and sonicated using sonicator for 2 h. Samples were filtered through 0.45µm filters and the solubility was measured by using UV spectrophotometer. Melting point: Melting point of Artesunate was determined by using melting point apparatus (dolphin). The drug was filled in a capillary tube and placed in the apparatus and the melting point was recorded.

Evaluation of micromeritic properties

Bulk density, tap density, Carr's index and Hausner's ratio: Bulk density and tap density were determined according to following method: A 50 ml glass cylinder was weighed and filled with 30 ml of Artesunate powder and reweighed. The opening was secured with parafilm. The cylinder was gently reversed once and the powder was carefully levelled without compacting. Bulk volume was determined after one mechanical tap on a tap density tester. Tap volume was measured after 2000 taps. [13-14] Values of bulk density and tap density are used to calculate Carr's index and Hausner's ratio and are given in Table 2.

$$\text{Bulk density} = \frac{\text{Weight of the powder}}{\text{Bulk volume}}$$

$$\text{Tap density} = \frac{\text{weight of the powder}}{\text{Tapped volume}}$$

$$\text{Carr's Index} = \frac{(\text{Tap density} - \text{bulk density})}{\text{Tap density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tap density}}{\text{Bulk density}}$$

Angle of repose

Fixed funnel method was used for determination of angle of repose and was calculated by using following formula. The values of angle of repose were as given in Table 2.

$$\text{Angle of repose} = \tan^{-1}(h/r)$$

Fourier transforms Infrared spectroscopy (FTIR)

Fourier transforms Infrared spectroscopy of Artesunate drug and polymers were recorded using Shimadzu FTIR system. Each spectrum was derived from single average scans collected in the region 4000 to 400 cm^{-1}. The FTIR spectra of drug and polymers are shown in given in figure 1 and 2 has confirmed the authentication of drugs. [14-16]

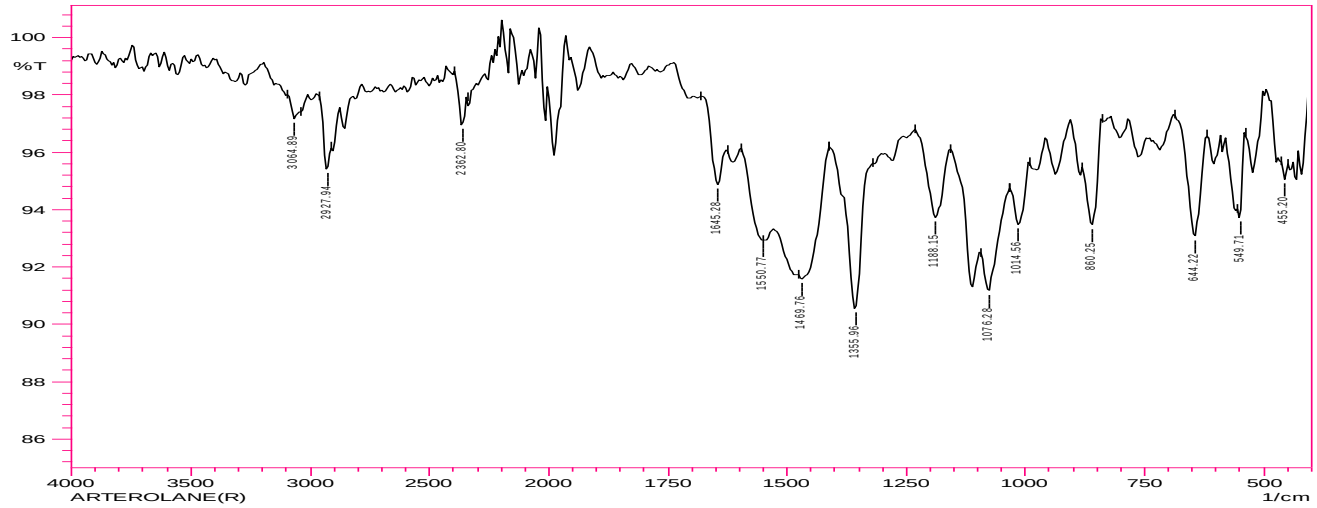

Fig. 1: FTIR of Artesunate

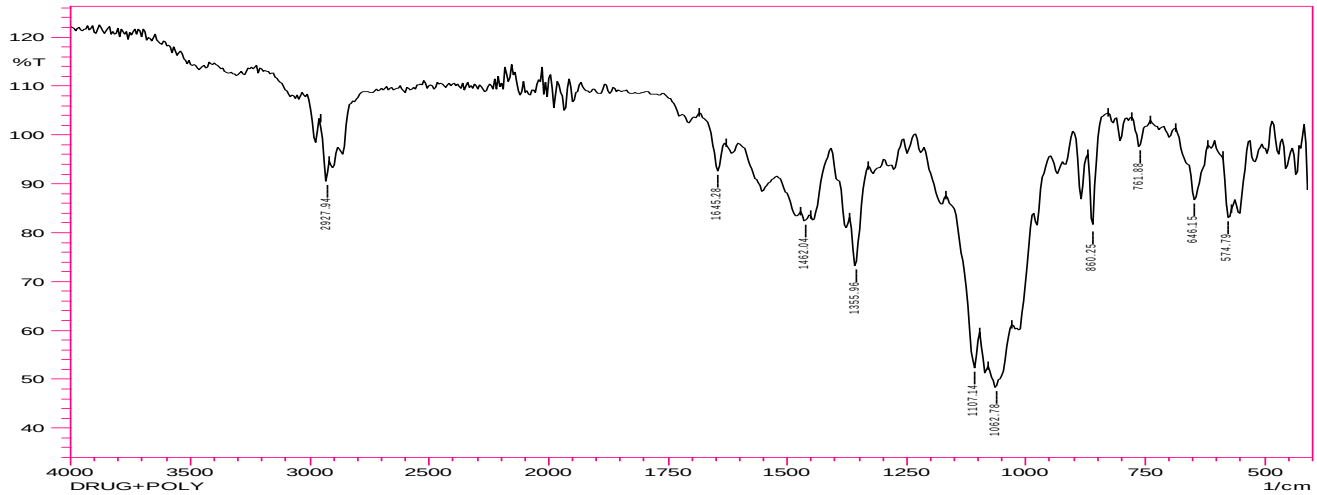

Fig. 2: FTIR of Formulation (with polymer)

Scanning Electron Microscopy (SEM)

The morphology of samples was carried out using SEM type II modes S-4800 Hitachi Japan. Surface morphology was analyzed at a working distance of 7-8.8 mm and 1.0 kv accelerating voltage. [16]

Particle Size Distribution and Zeta Potential

Particle Size Distribution and Zeta Potential were determined in water as a dispersion medium by laser diffraction size analyser and Malvern Zetasizer. [17]

Entrapment efficiency Studies

5 mg of pellets was diluted with 5% of methanol diluted with water and the absorbance was measured at 223 nm. The amount of Artesunate entrapped was determined by subtracting amount of free un-entrapped drug from the total amount of Artesunate taken for the preparation. The formula used to calculate entrapment efficiency is given below [18]

$$\text{Drug entrapment efficiancy} = \frac{\text{mass of drug in pellets}}{\text{mass of drug used in formulation}} \times 100$$

In-vitro dissolution studies

50 mg equivalent of microspheres were packed in hard gelatin capsules and were subjected to *in-vitro* dissolution studies using a twin buffer system consisting of 0.1 N HCl and 7.4 pH phosphate buffer using a USP I dissolution apparatus for a period of 24 hours. Samples were withdrawn at regular intervals while substituting the same with fresh buffer. Samples were suitably diluted and tested spectrophotometrically at λ_{max} of 223nm. The resultant values were taken and cumulative drug release percentage was calculated. [19-20]

RESULTS AND DISCUSSION

Physicochemical tests

Artesunate drug was characterised by various physicochemical tests. From the solubility studies it has been found that Artesunate is slightly soluble in water and freely soluble in methanol and chloroform. The melting point was found to be 142.16°C. Artesunate meets all the ideal characteristics to formulate in the form of oral drug delivery system.

FTIR studies

The compatibility of the drug and polymers were established through FTIR studies. Artesunate was identified by FTIR spectroscopy (Figure 1, 2) under Pre formulation study, FTIR between the drug and excipients showed no unaccountable extra peaks, which confirms the absence of chemical interaction between the drug and excipients/polymer. In the physical mixture of Artesunate, Ethyl cellulose and

MCC the major peaks found were 3319.02 cm^{-1} (N-H stretch), 1400.12 cm^{-1} (C-F stretch), 1349.50 cm^{-1} (C-O stretch) and 1375.32 cm^{-1} (N-O stretch) wave numbers. The result indicated that there was no chemical interaction between drug and polymers Table 2.

Table 2: Peaks observed in FTIR spectra of Artesunate and Formulation

Description	Pure drug (cm^{-1})	Formulation (cm^{-1})
N-H	3319.02	3291.10
C-F	1400.12	1435.15
C-O	1349.50	1352.41
N-O	1375.32	1370.18

Table 3: Characterization of Granules

S. No	Parameters	Observations
1	Bulk density (gm/cc)	0.544 ± 0.07
2	Tapped density (gm/cc)	0.591 ± 0.06
3	Carr's Index (%)	0.795 ± 0.50
4	Hausner's Ratio	1.086 ± 0.04
5	Angle of Repose (º)	22.23 ± 1.5°

Table 4: Entrapment efficiency

Formulations	Entrapment efficiency (%)*
F1	63.54 ± 0.43
F2	68.77 ± 0.25
F3	77.65 ± 0.71
F4	83.44 ± 0.08

*All the values are expressed as mean ± Standard deviation; n=3

Bulk Characterizations

Pellets containing Artesunate and polymer with different ratios (F1 to F4) were prepared by extrusion spheronization method. Physical properties such as particle size analysis, bulk density, Tapped density, and assay were evaluated and compiled in the table 3. The results were found satisfactory.

The shape and surface area of pellets was determined by scanning electron microscopy (Fig. 4, 5). The sizes of the pellets were ranging from 10-100µm. Further particle size distribution and zeta potential of pellets were studied and indicated that the combination product with the highest polymer ratio gave the best result of 3.70 mV. The percentage entrapment was calculated spechtrophotometrically. All the formulations showed various degrees of entrapment. The formulations F4 showed (Table 4) a better result and best entrapment.

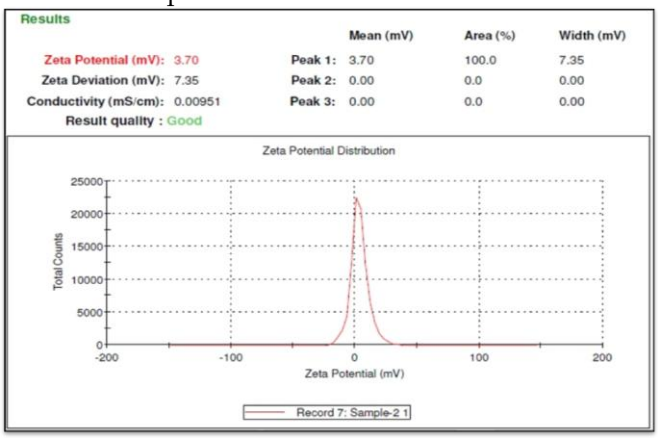

Fig. 3: Zeta potential result for formulation F4

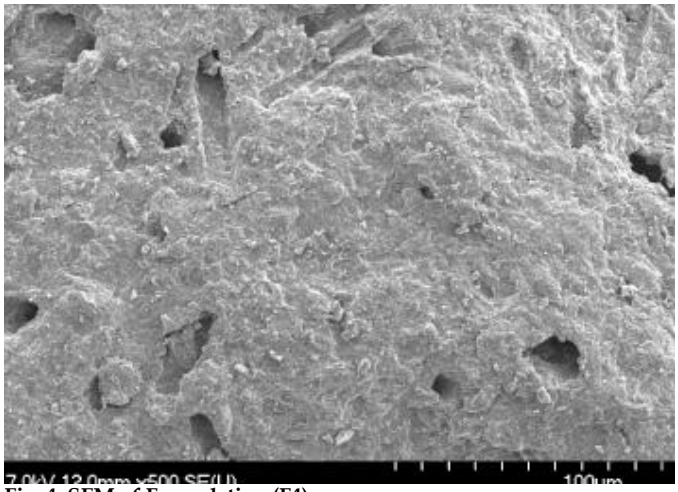

Fig. 4: SEM of Formulation (F4)

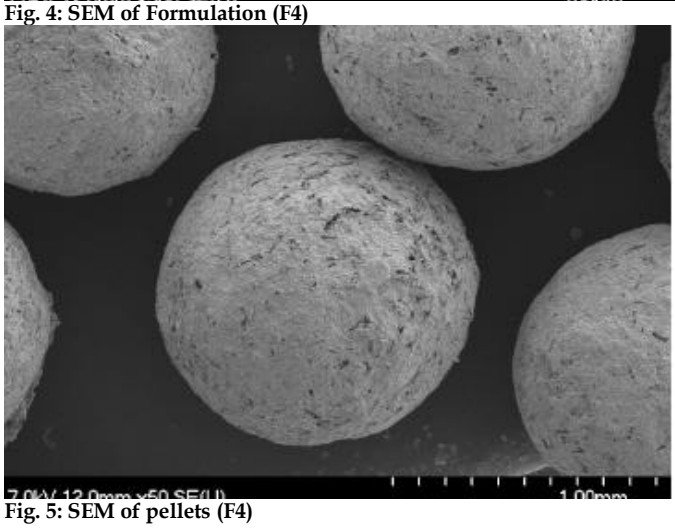

Fig. 5: SEM of pellets (F4)

Table 5: *In-vitro* Dissolution studies

S. No	Time (hrs)	% cumulative drug release			
		F1	F2	F3	F4
1	1	13.12 ± 0.12	21.45 ± 0.07	18.90 ± 0.11	13.12 ± 0.12
2	3	23.45 ± 0.27	35.75 ± 0.23	27.35 ± 0.27	25.45 ± 0.27
3	6	63.21 ± 0.28	63.75 ± 0.14	65.19 ± 0.28	67.21 ± 0.28
4	12	66.65 ± 0.25	85.44 ± 0.23	75.65 ± 0.27	79.65 ± 0.25
5	16	82.23 ± 0.15	86.31 ± 0.16	84.25 ± 0.17	84.23 ± 0.15
6	20	87.43 ± 0.23	86.99 ± 0.48	87.45 ± 0.43	88.43 ± 0.23
7	24	87.85 ± 0.10	87.63 ± 0.23	88.67 ± 0.06	90.95 ± 0.12

In vitro release studies

The *in-vitro* dissolution studies which were carried out for a period of 24 hours using a twin buffer system showed a minimal drug release during the initial stages for all the formulations. By mixing various hydrophilic polymers with MCC may aid in extrusion-spheronization and, at the same time, to enhance the dissolution of Artesunate. Therefore, the aim of studying in *vitro* release from matrix pellets is to investigate the effect of different concentration of Ethyl cellulose on the drug release patterns. Incorporation of the drug in pellet formulations composed of MCC only resulted in slowing its release rate. (Table 5, Fig. 6) The

best formulation was found to be F4 which showed a cumulative drug release of 90.95 ± 0.12% at the end of the study.

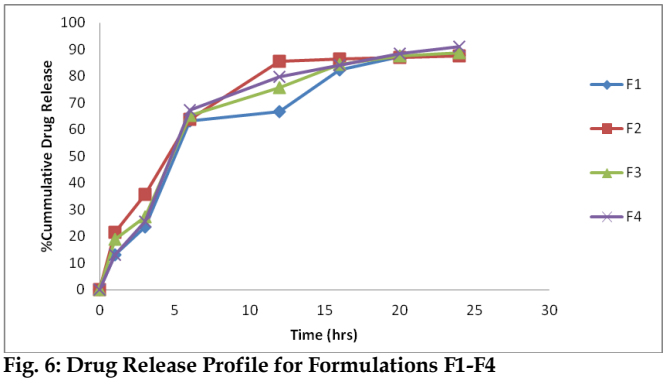

Fig. 6: Drug Release Profile for Formulations F1-F4

Pellets were formulated using extrusion spheronizaion technique. The Formulations were prepared using different polymer ratios. The FTIR results concluded that there are no chemical interactions between drug and polymers. Scanning electron microscopy was done which shows the formation of pellets. The pellets were formed in the size range of 10-100µm. Further particle size distribution and zeta potential of pellets were studied and indicated that the combination product with the highest polymer ratio gave the best result of 3.70 mV. Dissolution studies were carried out using a twin buffer system showed a minimal drug release during the initial stages for all the formulations and gradual increase during the later stages of the process.

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