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Evaluation of dispersible tablets of antimalarial drug combination - artemether and lumefantrine

Kerryn Joseph A D'Silva[1], Suresh N[2]*, Preethi Fernandiz[3]

[1]*Department of Pharmaceutical Chemistry, D.R. Karigowda College of Pharmacy, Hassan, Karnataka – 573201*

[2]*Department of Pharmaceutics, D.R. Karigowda College of Pharmacy, Hassan, Karnataka – 573201*

[3] *Department of Pharmacy Practice, D.R. Karigowda College of Pharmacy, Hassan, Karnataka – 573201*

Corresponding author: Suresh N

Email: sureshsudha1975@gmail.com

ABSTRACT

More patient compliance dose forms have been in high demand for the previous two decades. As a result, the demand for technology is growing at a three-fold yearly rate. In the pharmaceutical business, oral delivery is currently the gold standard, as it is recognised as the safest, most convenient, most cost-effective route of drug delivery with the best patient compliance.

Tablets and capsules are the most common dose forms; nonetheless, one significant disadvantage of these dosage forms is their difficulty in swallowing. To address this flaw, scientists have created dispersible tablets, which are novel medication delivery mechanisms.

The main aim of this work is to evaluate the dispersible tablets of Artemether and Lumefantrine formulated using co-processed superdisintegrants containing crospovidone and sodium starch glycolate. Further, the dispersible tablet formulations were subjected to their stability studies for two months and again subjected to further evaluation tests.

Results revealed that all the formulated tablets have acceptable physical properties. *In-vitro* studies revealed that the drug released by F9 formulation (sodium starch glycolate and crospovidone in 1:3) is comparatively higher release than the other formulations. The formulation F9 shows the release of Artemether 91.03% and release of Lumefantrine 90.45% these results were found to be satisfactory. To analyze the mechanism of drug release from the dispersible tablets, the *in-vitro* drug release data was fitted to Zero order, First order, Higuchi equation, Hixon-Crowel and Koresmeyers-Peppas model. It was observed that the release of the drug followed the First order in all the formulations and the "n" value indicates that the release mechanism follows Fickian release.

Thus, it can be summarized that stable Artemether and Lumefantrine dispersible tablets were prepared successfully by using co-processed superdisintegrants by direct compression method to enhance the dissolution rate.

Keywords: Dispersible tablets, Artemether, Lumefantrine, Evaluation.

INTRODUCTION

Malaria is a common and life-threatening disease in many tropical and subtropical areas. There are currently over 100 countries and territories where there is a risk of malaria transmission, and these are visited by more than 125 million international travellers every year. Malaria is caused by the protozoan parasite Plasmodium. Human malaria is caused by four different species of *Plasmodium: P. falciparum, P. malariae, P. ovale and P. vivax*. Humans occasionally become infected with Plasmodium species that normally infect animals, such as *P. knowlesi.*(1)

The natural history of malaria involves cyclical infection of humans and female *Anopheles* mosquitoes. In humans, the parasites grow and multiply first in the liver cells and then in the red cells of the blood. In the blood, successive broods of parasites grow inside the red cells and destroy them, releasing daughter parasites ("merozoites") that continue the cycle by invading other red cells.

The blood-stage parasites are those that cause the symptoms of malaria. When certain forms of blood-stage parasites (gametocytes, which occur in male and female forms) are ingested duringblood feeding by a female *Anopheles* mosquito, they mate in the gut of the mosquito and begin a cycle of growth and multiplication in the mosquito. After 10-18 days, a form of the parasite called a sporozoite migrates to the mosquito's salivary glands. When the *Anopheles* mosquito takes a blood meal on another human, anticoagulant saliva is injected together with the sporozoites, which migrate to the liver, thereby beginning a new cycle.

Thus the infected mosquito carries the disease from one human to another (acting as a "vector"), while infected humans transmit the parasite to the mosquito, in contrast to the human host, the mosquito vector does not suffer from the presence of the parasites.(2)

Drug administration by oral route has wider acceptance than other dosage forms. Among all solid dosage forms, tablets are the most popular because of ease of administration, easy manufacturing, compactness, accurate dosage, self-administration and most importantly the patient compliance.It may sometimes be inconvenient to swallow a conventional product due to the unavailability of water which leads to poor patient compliance(3).

Recent advances in novel drug delivery system (NDDS) aims to enhance safety and efficacy of drug molecules by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is a mouth dissolving tablet. The concept of mouth dissolving drug delivery System emerged from the desire to provide the patient with a conventional mean of taking their medication(4).

The dispersible tablets allow dissolution or dispersion in water before administration but the mouth dissolving tablet instead of dissolving or disintegrating in water is expected to dissolve or disintegrate in the oral cavity without drinking water. According to European Pharmacopoeia, the orodispersible tablet (ODT) should disperse/disintegrate in less than three minutes. The basic approach in the development of FDT (Fast dissolving tablets) is the use of superdisintegrants like cross-linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinylpyrrolidone (polyplasdone) etc, which provide instantaneous disintegration of the tablet(5).

Mouth dissolving drug delivery systems (MDDS) is a new generation of formulations that combine the advantages of both liquid and conventional tablet formulations, and at the same time, offer added advantages over both the traditional dosage forms. They provide the convenience of a tablet formulation and also allow the ease of swallowing provided by a liquid formulation(6).

Advantages of orally disintegrating drug delivery system(5,7)

- Administration to the patients who cannot swallow, such as the elderly, stroke victims,bed ridden patients, patients affected by renal failure and patients who refuse to swallow such as pediatric, geriatric and psychiatric patients.
- Rapid drug therapyintervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx and oesophagus as saliva passesdown.
- Convenient for administration and patient compliance for disabled, bedridden patients and for travellers and busy people, who do not always have access to water.

MATERIALS AND METHODS

Artemether and Lumefantrine were obtained as a gift sample obtained from Strides Arcolab Limited, Bangalore. Crospovidone, Microcrystalline cellulose, Croscarmellose sodium, Magnesium stearate, Hypromellose, Silica colloidal anhydrous, Polysorbate 80, Sodium saccharin, Mannitol was purchased from S.D fine chem limited, Mumbai. All chemicals were of analytical grade.

Evaluation of blended characteristics of artemether and lumefantrine combination

Evaluation of Granules

Determination of angle of repose(8)

The angle of repose is an indication of the frictional forces excited between granule particles. It is the maximum angle possible between the surface of the pile of granules and the horizontalplane:

$$\mathbf{Tan\ \theta = h/r}$$

Where, θ = the angle of repose
h = height of the heap of the powder
r = radius of the heap of the powder

Method

Weighed quantities of powder (mix blend) were poured through the funnel from the fixed height onto the graph paper. The height of the heap was measured. The circumference of the heap was marked by pencil. The area of the circle formed was calculated based on large squares and small squares present inside the circle and the angle of repose was then calculated on the parameter "r" which was found out from the area of the circle.

Determination of Bulk Density and TappedDensity(8)

20 g of the mixed blend (W) was introduced into a 100 ml measuring cylinder, and the initial volume was observed. The cylinder was allowed to fall under its weight onto a hard surface from the height of 2.5 cm at 2-sec intervals. The tapping was

Bulk density = W / VO

Tapped density = W / VF

continued until no further change in volume was noted. The bulk density and tapped density were calculated using the following formulae.
Where, W = weight of the granules, VO = initial volume of the granules, VF = final volume of the granules.

Hausner's Ratio:(8)

It indicates the flow properties of the granules and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

Compressibility index (Carr's Index):(8)

The compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20% has good flow property.

$$CI = \frac{TAPPED\ DENSITY - BULK\ DENSITY}{TAPPED\ DENSITY}\ X\ 100$$

Post-compression Parameters

Evaluation of Artemether and Lumefantrine dispersible tablets

Tablets were subjected to evaluation parameters including drug content uniformity, weight variation, tablet hardness, friability thickness, and in-vitro drug release with different media.

Taste, colour, the odour of tablets (8)

Organoleptic properties such as taste, colour, odour were evaluated ten tablets from each batch were randomly selected and taste-tested, colour visually compared and odour checked.

Weightvariation(8)

The weight of the tablet being made was routinely determined to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablets met the USP specification that not more than 2 tablets are outside the percentage limits and no tablet differs by more than 2 times the percentage limit.

Tablethardness(8)

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using the Monsanto hardness tester. The hardness was measured in terms of N (Newton). 5 tablets were chosen randomly and tested for hardness. The average hardness of 5 determinations was recorded.

Friability(8)

Method: 20 tablets were weighed and the initial weight of these tablets was recorded and placed in Roche friability and rotated at the speed of 25 rpm for 100 revolutions. Then tablets were removed from the friabilator dusted off the fines and again weighed and the weight was recorded.
Percentage friability was calculated by using the formula:

$$\%\ Friability = \frac{\text{The initial weight of the tablets} - \text{Final weight of the tablets}}{\text{The initial weight of the tablets}}\ X\ 100$$

Tabletthickness(8)

The thickness of the tablet is important for the uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking the thickness of ten tablets of each formulation.

Content Uniformity ofArtemether(8)

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg was weighed accurately and dissolved in 100 ml of 0.5% of SLS phosphate buffer. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 211 nm. The concentration of the drug was computed from the standard curve of the Artemether in 0.5% of the SLS phosphate buffer.

Content Uniformity of Lumefantrine(8)

The tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg was weighed accurately and dissolved in 100 ml of 0.1 N HCl containing 0.5% Tween 80. The solution was shaken thoroughly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Then the serial dilutions were carried out. The absorbance of the diluted solutions was measured at 342 nm. The concentration of the drugwas computed from the

standard curve of the Lumefantrine in 0.1 N HCl containing 0.5% Tween 80.

Disintegration time(8)

Tablet disintegration is an important step in drug absorption. The disintegration test was carried out in the Electro lab USP disintegration test apparatus. It consists of 6 glass tubes that are 3 inches long, open at the top, and held against a 10 mesh screen, at the bottom end of the basket rack assembly. To test the disintegration time of tablets, one tablet was placed in each tube and the basket rack was positioned in a 1-litre beaker containing 0.5% of SLS in water at 37 oC ± 2 °C such that the tablet remains 2.5 cm below the surface of the liquid. The time taken for the complete disintegration of the tablets was noted.

Wetting time(9)

10 ml of distilled water containing Eosin, a water-solubledye was placed in a petri dish of 10 cm diameter. Tablets were carefully placed in the centre of the petri dish and the time required for water to reach the upper surface of the tablet was noted as the wetting time. The test results are presented as the mean value of three determinations.

Water absorptionratio(9)

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 and the time required for complete wetting was measured. The wetted tablet was then weighed. The water absorption ratio indicated by R, which is calculated by using the below-mentioned equation.

$$R = (W_a - W_b / W_b)\ 100$$

In-Vitro Dissolution Studies

In-vitro dissolution for Artemetherstudies(10,11)

Dissolution testing of Artemether was determined using USP dissolution apparatus. The paddle was used to rotate 100 rpm and temperature 37 ± 0.5 ^{O}C in 0.5% SLS phosphate buffer. At each specified intervals of time,a 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by the UV spectroscopy method at a wavelength of 211 nm.

In-vitro dissolution of Lumefantrine studies(10,11)

Dissolution testing of Lumefantrine was determined using the USP dissolution apparatus. The paddle was used to rotate 100 rpm and temperature 37 ± 0.5 °C in 0.1 N HCl and 0.5% Tween 80. At each specified intervals of time,a 5 ml sample was withdrawn and replaced by fresh media. The samples were analytically tested to determine the concentration by the UV spectroscopy method at a wavelength of 342 nm.

Mathematical modelling of drug release profile:(12)

The cumulative amount of Artemether and Lumefantrine 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 the mechanism of drug release.

Zero Order Kinetics

It describes the system in which the release rate is independent of its concentration.

$$Q_t = Q_0 + K_0 t$$

Where, Q_t = amount of drug dissolved in time t Q_0 = initial amount of drug in the solution K_0 = zero-order release constant
If the zero-order drug release kinetic is obeyed, a plot of Q_t versus t will give a straight line with a slope of K_0 and an intercept at Q_0

First Order Kinetic

It describes the drug release from the system in which the release rate is concentrated, dependant.

$$\log Q_t = \log Q_0 + K_1 t/2.303$$

Where Q_t = amount of drug dissolved intime
Q_0 = initial amount of drug in the solution
K_1 = first-order release constant

If the release pattern of the drug follows first-order kinetics, then a plot of log (Q_0 - Q_t) versus t will be a straight line with a slope of $K_1/2.303$ and an intercept at t= 0 of logQ_0.

Higuchi Model

It describes the fraction of drug release from a matrix that is proportional to the square root of time.

Where,

$$M_t/M_\infty = K_H\, t^{1/2}$$

M_t and M_∞ are cumulative amounts of drug release at time t and infinite time, and K_H = Higuchi dissolution constant reflection formulation characteristics.
If the Higuchi model of drug release is obeyed, then a plot of M_t/M_∞ versus $t^{1/2}$ will be a straight line with a slope of K_H.

Korsmeyer-Peppas Model

The power law describes the fractional drug release is exponentially related to the release time and adequately describes the release of drug from slabs, cylinders and spheres, as expressed in the following equation:

$$M_t / M_\infty = K\, t^n$$
$$\text{Log}\,(M_t / M_\infty) = \log K + n \log t$$

Table No 1: Mechanism of Drug Release as per Korsmeyer Equation/ Peppa's Model

SL. No	'n' value	Drug release
1.	0.45	Fickian release
2.	0.45 <n<0.89	Non- Fickian release
3.	n>0.89	Case II transport

Stability Studies(13)

Stability can be defined as the capacity of the drug product to remain within specifications established to ensure its identity, strength, quality, and purity.
Stability studies are done to understand how to design a product and its packaging such that the product has appropriate physical, chemical and microbiological properties during a defined shelf life when stored andused.
The optimized formulation was subjected to two months stability study according to ICH guidelines. The selected formulations were packed in aluminium foil in a tightly closed container. They were then stored at 40 ^{O}C / 75% RH for two months and evaluated for their permeationstudy.

RESULTS AND DISCUSSION

Post- Compression Evaluation Parameters

Various standards or quality control test carried out on compressed tablets demonstrated the following.

General appearance

All the dispersible tablets formulations were evaluated for their general appearances like taste, colour and odour. All Dispersible tablets formulation isthe sweet taste, yellow colour and Mint odour.

Thickness of tablets

All the dispersible tablet formulations were evaluated for their thickness using Vernier callipers as per procedure in methodology.The average thickness for all the formulations was found to be within the allowed limit of deviation i.e. 5% of the standard value. Also, the crown diameter of all the formulation was 14 mm.

Hardness

Tablet hardness is a critical parameter to evaluate the resistance of tablets to capping, abrasion or breakage under conditions of storage, transportation and handling before usage. All the dispersible tablet formulations were evaluated for their hardness as per the procedure in methodology. All the formulations have an average hardness between 53 N to 73 N which was found to be acceptable; because these formulations have to be disintegrated on the tongue between 25 seconds to 1 minute. So an excess of hardness is not favoured for these formulations. The hardness for F9 (73 ± 3N) was found to be highest of all formulations and for F2 (55 ± 5N) was found to be the least and the control formulation F1 which shows (56 ± 2) values respectively for the aboveparameters.

Friability

Friability is determined to evaluate the ability of the tablets to withstand abrasion in packing, handling and transporting. All the Dispersible tablet formulations were evaluated for their percentage friability as per the procedure in methodology.The average percentage friability for all the formulations was between 0.18% to 0.90%,which was found to be within the limit (i.e. maximum 1%). So, the maximum friability was 0.90% and the minimum friability0.18%observed for F4 and F9 respectively and control formulation F1 which shows 0.38% values respectively for the above parameters.

Wetting Time

Wetting time is another important related parameters to water absorption, which needs to be assessed to give an insight into the disintegration properties of tablets. The

wetting time corresponds to the time taken for the tablet to disintegrate when motionless on the tissue paper in a Petri dish. This method will duplicate the *in-vivo* disintegration, as the tablet is kept motionless on the tongue. All the formulated dispersible tablets of Artemether and Lumefantrine were evaluated for their wetting time as per the procedure in methodology.The average wetting time for all the formulations was in the range of 28 to 39 seconds. The maximum wetting time of 39 seconds and minimum wetting time of 28 seconds was shown by F3 and F9 respectively and control formulation F1 which shows 55 seconds values respectively for the above parameters.

Weight Variation

As the material was free-flowing tablets obtained were uniform weight due to uniform die fill with acceptable variation as per IP standards. All the dispersible tablet formulations were evaluated for their uniformity of weight according to the procedure described in the methodology. The maximum weight was 404.60±0.60 for F8 and the minimum observed was 397.93±0.36 for F2. The maximum allowed percentage weight variation for tablets 80-250 mg by I.P is 7.5%, and no formulations are exceeding this limit. Thus, all the formulations were found to comply with the standards given inIP.

Drug Content

Uniformity of drug content test is applicable for tablets that contain less than 10 mg or less than 10% w/w of the active ingredient. The test for uniformity of drug content should be carried out only after the content of active ingredient in a pooled sample of tablets is within the accepted limit of the stated amount. All the dispersible tablet formulation were evaluated for their uniformity of drug content according to the procedure described in the methodology. The range of uniformity of drug content for all formulations of Artemether was 95.92% w/w to 97.90% w/w respectively and control formulation F1 which shows 93.51% w/w values respectively and the range of uniformity of drug content for all formulations of Lumefantrine was 98.27% w/w to 98.95% w/w respectively and control formulation F1 which shows 98.20% w/w values respectively for the above parameters. Thus, all the formulations were found to comply with the standards given inIP.

In-vitro disintegration time

Disintegration, the first important step for drug absorption from a solid dosage form after oral administration was preliminarily focused. An important factor affecting the disintegration is the hardness and influences on the disintegration time as it affects the porosity of the matrix and accordingly the ability of water to penetrate through the matrix. All the dispersible tablet formulations were evaluated for their *in-vitro* disintegration time to the procedure described in the methodology. The average *in-vitro* disintegration time for all the formulations was in the range of was 25 to 53 seconds and control formulation F1 which shows 240 seconds. The *in-vitro* disintegration time for formulation F9 was 25 sec andthe highest disintegration time was found to be formulation F4 was 53 seconds. So the amount of water uptake and swelling will be more for this formulation F9 and this increased disintegration.

Water absorption ratio

To investigate the importance of the total surface area in promoting drug dissolution, a water uptake study was performed on Artemether and Lumefantrine dispersible tablets. Since the drug has to dissolve from the interface between drug and water, the maximal water uptake volume can be taken as an estimation of the total surface area available for drug dissolution to take place. All the dispersible tablet formulations were evaluated for their water absorption ratio and the procedure is described in the methodology. The average water absorption ratio for all the formulations was in the range of 50.75% to 64.58% and control formulation F1 shows 39.51% for the above parameters. The water absorption ratio was found to be less in formulation F10 (50.75%) and more water absorption ratio was found to be in formulation F9 (64.78%).

Table no 2: Post- Compression Evaluation Parameters

Code	Weight variation (mg)	Hardness (N)	Thickness (mm)	Friability (%)	Artemether Drug content (%)	Lumefantrine Drug content (%)	Disintegration Time (sec)	Wetting time	Water absorption ratio	% CDR Artemether	% CDR Lumefantrine
F1	399.98 ± 0.22	36	4.12±0.01	0.38±0.15	93.51±0.57	98.20±0.76	240	55	39.95	13.33	13.78
F2	397.93 ± 0.36	55	4.15±0.03	0.76±0.11	95.92±0.42	98.27±0.76	40	36	50.8	74.80	74.83
F3	401.21 ± 0.49	64	4.15±0.03	0.77±0.09	96.75±0.32	98.53±0.89	49	39	57.8	80.23	80.13
F4	400.92 ± 0.41	68	4.14±0.02	0.90±0.62	97.5±0.27	98.35±0.78	53	36	55.84	78.73	78.83
F5	402.16 ± 0.32	71	4.14±0.01	0.41±0.44	96.20±0.89	98.64±0.42	30	32	59.42	81.90	81.83
F6	397.95±0.91	69	4.15±0.04	0.92±0.53	96.85±0.42	98.39±0.78	33	34	55.18	79.59	79.58
F7	400.51±0.99	63	4.12±0.01	0.37±0.20	96.57±0.84	98.69±0.42	39	33	59.65	77.77	77.61
F8	404.60±0.60	73	4.14±0.02	0.40 ±0.32	97.87±0.42	98.74±0.41	28	28	62.08	88.16	88.10
F9	400.01±0.59	66	4.14±0.01	0.18±0.06	97.90±0.42	98.95±0.35	24	20	64.58	91.03	90.45
F10	401.51±1.02	61	4.15±0.01	0.33±0.09	97.31±0.16	98.83±0.56	29	31	50.75	84.01	83.98
F11	400.03±0.59	69	4.14±0.01	0.66±0.09	95.74±0.57	98.76±0.41	31	30	54.45	85.60	85.40

In-vitro drug release studies

As there is no specific dissolution test available for dispersible tablets dissolution rate is studied as per USP specifications for conventional tablets with little modification. All the dispersible tablet formulations were evaluated for their *in-vitro* drug release according to the procedure described in the methodology.

The maximum drug release of Artemether 91.03% was obtained from formulation F9, and the minimum drug release of Artemether 74.80% shown by F2. The average drug release immediately after dispersion for all the formulations was in the range of 74.80% to 91.03%. The control formulation F1 drug release was found to be 13.3%.

The maximum drug release of Lumefantrine 90.45% was obtained from formulation F9, and the minimum drug release of Lumefantrine 74.83% shown by F2. The average drug release immediately after dispersion for all the formulations was in the range of 74.83% to 91.45%. The control formulation F1 drug release was found to be 13.78%.

The formulation F9 containing co-processed superdisintegrants sodium starch glycolate: crospovidone (1:3) enhanced the dissolution rate of dispersible tablets.

Table no 3: *In-vitro* drug releasestudies of Artemether

Sl.no	Time in mins	% CUMULATIVE DRUG RELEASE											
		FORMULATION CODE											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	MP
1	0.5	5.4	31.5	36.5	39.5	39	39.75	37.75	45.25	46.25	40.25	44.75	34.25
2	1	6.0	59.42	59.45	56.96	51.96	49.47	51.95	54.50	56.50	53.47	52.74	47.44028
3	1.5	6.57	65.0	68.28	68.28	63.25	60.74	57.99	70.80	73.31	67.76	69.79	59.70278
4	2	7.07	68.11	73.15	71.91	70.6	68.07	65.56	75.94	80.72	73.64	72.92	65.28194
5	3	7.53	70.23	75.3	76.05	73.24	72.70	70.92	79.60	83.66	75.54	78.32	70.14028
6	4	9.67	72.36	76.97	77.47	75.39	75.35	72.31	82.54	85.12	78.45	81.25	76.02361
7	6	10.9	73.26	78.13	78.39	78.05	77.00	74.95	84.74	87.08	80.38	83.69	80.4375
8	8	12.0	73.90	79.06	78.56	79.97	78.42	76.61	86.95	89.05	82.32	84.89	82.87361
9	10	13.3	74.80	80.23	78.73	81.90	79.59	77.77	88.16	91.03	84.01	85.60	85.07083

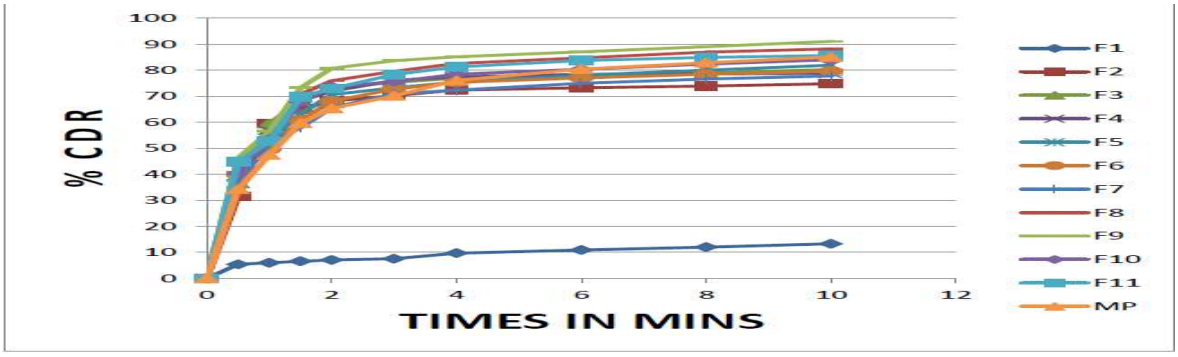

Figure 1: *In-vitro* drug release studies of Artemether

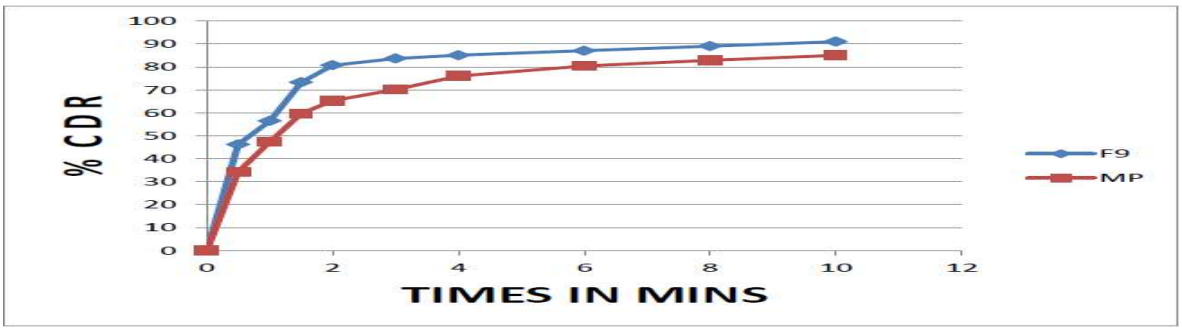

Figure 2: Best formulation F9 comparison with marketed product

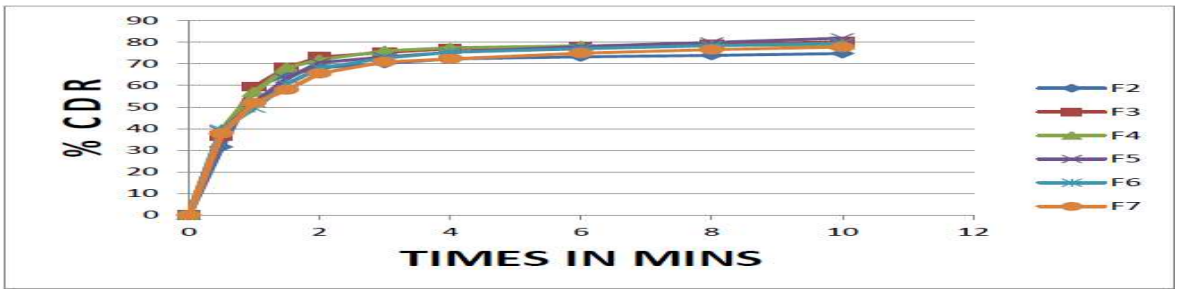

Figure 3: *In-vitro* Artemether release comparison of co-processed superdisintegrants with a physical mixture containing CP

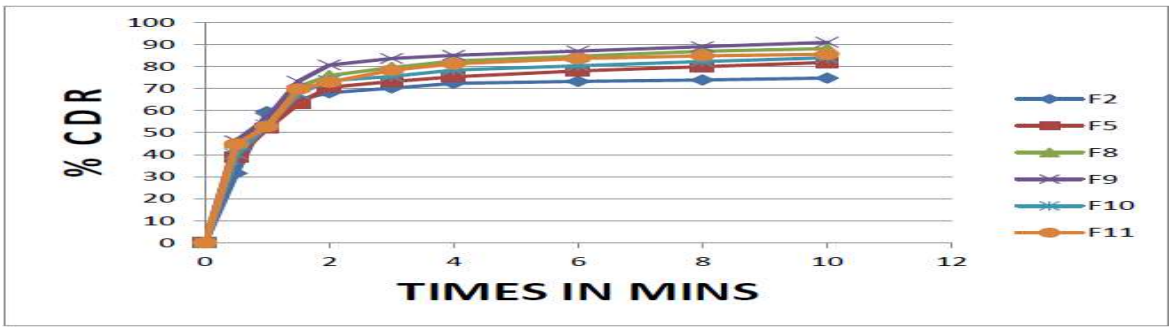

Figure 4: *In-vitro* Artemether release comparison of co-processed superdisintegrants with a physical mixture containing SSG

Table no 4:*In-vitro* drug release studies of Lumefantrine

Sl.no	Time in mins	% CUMULATIVE DRUG RELEASE											
		FORMULATION CODE											
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	MP
1	0.5	5.2	31.0	36.4	39.4	39	39.65	37.61	45.20	46.31	40.25	44.70	34.00
2	1	6.1	59.13	59.36	56.86	51.79	49.51	51.81	54.46	56.52	53.49	51.86	46.9124
3	1.5	6.47	64.90	68.31	68.10	63.10	60.47	57.99	70.08	73.13	67.67	69.80	59.6829
4	2	7.05	68.08	73.01	71.81	70.51	68.70	65.65	75.49	80.27	73.46	72.81	65.2614
5	3	7.45	70.16	75.4	75.96	73.13	72.07	70.29	79.06	83.66	75.45	78.61	70.1408
6	4	9.53	72.45	76.89	77.31	75.61	75.53	72.13	82.45	85.21	78.54	81.01	76.0101
7	6	10.7	73.31	78.10	78.39	78.09	77.20	74.59	84.47	87.80	80.83	83.10	80.4128
8	8	12.3	73.96	79.00	78.61	79.78	78.16	76.52	86.81	88.95	81.91	84.50	82.8531
9	10	13.78	74.83	80.13	78.83	81.83	79.58	77.61	88.10	90.45	83.98	85.40	85.0162

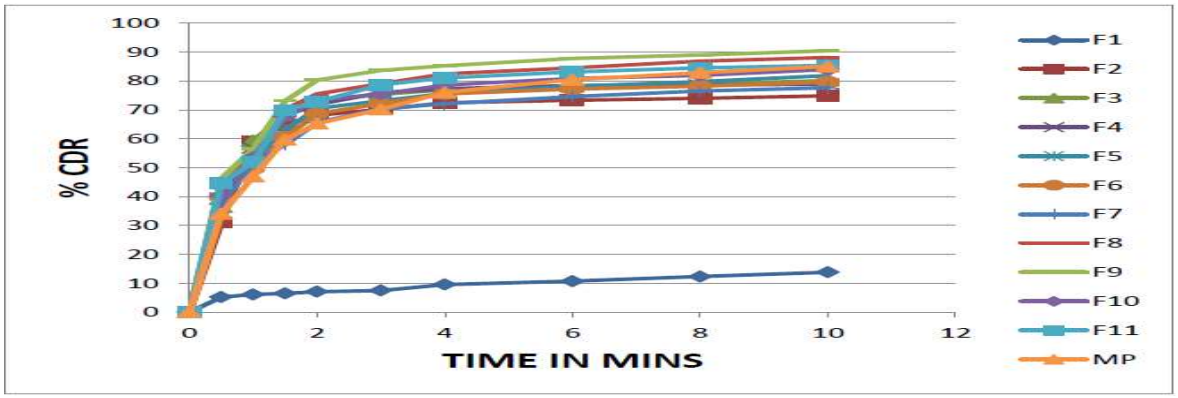

Figure 5: *In-vitro* drug release studies of Lumefantrine

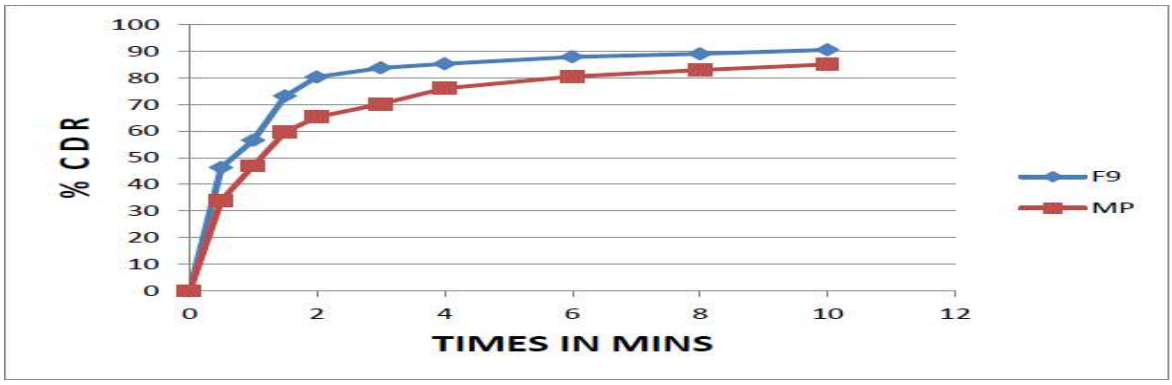

Figure 6: Best formulation F9 comparison with marketed product

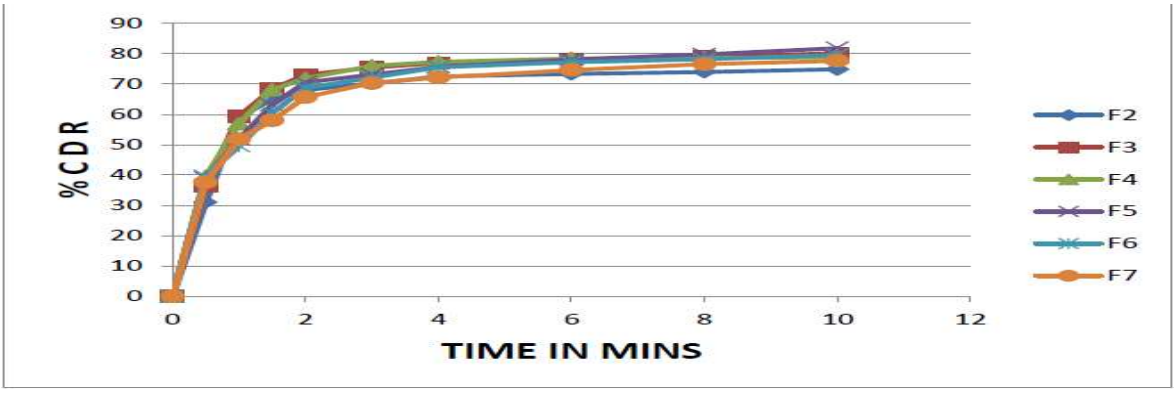

Figure 7: *In-vitro* Lumefantrine release comparison of co-processed superdisintegrants with a physical mixture containing CP

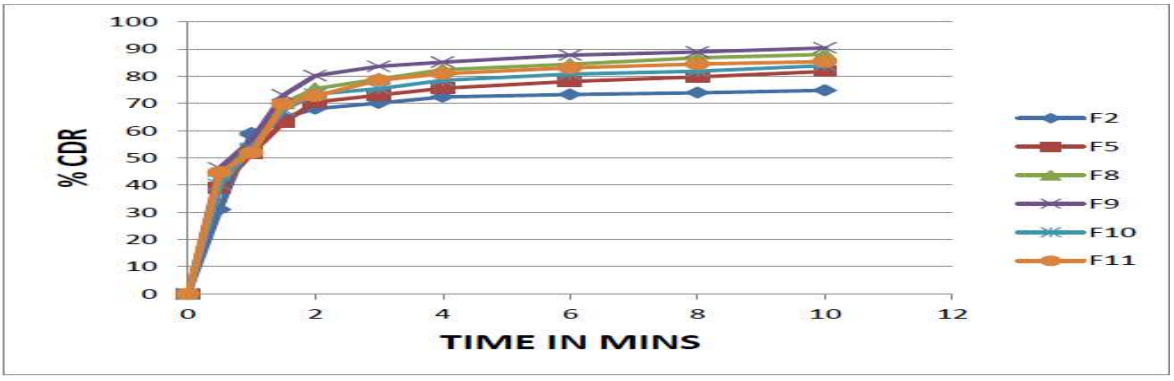

Figure 8: *In-vitro* Lumefantrine release comparison of co-processed superdisintegrants with a physical mixture containing SSG

Discussion about kinetic models

Different kinetic equations (Zero order, First order, Higuchi's, Hixson-Crowell and Koresmeyer-Peppas equation) were applied to interpret the release rate.

The release obeyed first-order kinetics and the results of this investigation showed a high correlation coefficient among the formulation for first-order release and the probable release mechanism was initial diffusion and the value of release exponent (n) was found to be a function of the polymer used and the physicochemical properties of the drug molecule itself and the n values was found to be in the range of 0.113 to 0.348 followed with Fickian (case I) release.

Stability Studies Results

Table 5: Release exponent values and release rate constant values for a different formulation

Formula code	Koresmeyar and peppas		Higuchi	Hixon crowel	First-order	Zero-order
	R^2	n	R^2	R^2	R^2	R^2
F1	0.967	0.348	0.981	0.975	0.975	0.973
F2	0.635	0.130	0.559	0.492	0.534	0.414
F3	0.706	0.122	0.62	0.557	0.604	0.468
F4	0.746	0.113	0.632	0.539	0.572	0.473
F5	0.849	0.129	0.773	0.722	0.769	0.627
F6	0.869	0.128	0.780	0.704	0.740	0.630
F7	0.868	0.127	0.794	0.723	0.760	0.647
F8	0.855	0.119	0.769	0.739	0.797	0.623
F9	0.828	0.117	0.730	0.711	0.779	0.582

F10	0.823	0.126	0.738	0.692	0.744	0.589
F11	0.855	0.119	0.765	0.713	0.760	0.616
F12	0.772	0.164	0.717	0.653	0.696	0.565

R^2=Regression coefficient, n= Exponential value

The stability studies for best formulations were carried out as per procedure in methodology.There was no significant change in taste, colour and odour. The results found to be satisfactory.

Table 6: Stability studies for best formulations stored at 40ºC/75% RH

TIME	Hardness kg/cm^2		Drug content		*In-vitro* drug release (%CDR)	
	F8	F9	F8	F9	F8	F9
15 days	3.14	3.05	97.87	98.79	88.16	91.03
30 days	3.12	3.05	97.57	98.33	87.91	90.82
45 days	3.13	3.01	97.22	98.05	87.07	90.55
60 days	3.1	3.0	96.9	97.77	86.84	90.00

Stability studies

A stability study was conducted for the two best formulations selected based on *in-vitro* disintegration time and *in-vitro* drug release. The stability studies were conducted according to the described methodology. There was no significant reduction in the drug release profile of formulation F9 no significant taste, colour and odour changes. There was no significant variation in the drug content and *in-vitro* dissolution profiles after two months of stability study for best formulations F9 thus specialized pickings and storage conditions are necessary for the prepared dispersible tablets of Artemether and Lumefantrine combination.

CONCLUSION

It can be concluded from the present work that co-processed superdisintegrants of crospovidone and sodium starch glycolate are superior to a physical mixture of crospovidone and sodium starch glycolate used in Artemether and Lumefantrine dispersible tablets by direct compression method. The Artemether and Lumefantrine dispersible tablets were found to have an enhanced dissolution rate.

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