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Formulation of dispersible tablets of antimalarial drug combination - Artemether and Lumefantrine

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ABSTRACT

For the past two decades, there is an enhanced demand for more patient compliance dosage forms. As a result, the demands for the technologies are increasing three folds annually. Oral delivery is currently the golden standard in the pharmaceutical industry where it is regarded as the safest, most convenient and economical method of drug delivery having the highest patient compliance. The most popular dosage forms being tablets and capsules, one important drawback of these dosage forms however is the difficulty to swallow. To overcome this weakness, scientists have developed innovative drug delivery systems known as dispersible tablets.

The main aim of this work is to prepare and evaluate dispersible tablets of Artemether and Lumefantrine using co-processed super disintegrants containing crospovidone and sodium starch glycolate. Ten batches of dispersible tablets Artemether and Lumefantrine along with control formulation tablets were prepared by direct compression method using conventional tabletting equipment and subjected to various evaluation tests. All the formulations were evaluated for pre-compression and post-compression parameters. Results revealed that all the formulated tablets have acceptable physical properties. Thus, it can be summarized that stable Artemether and Lumefantrine dispersible tablets were prepared successfully by using co-processed superdisintegrants by direct compression method.

Keywords: Dispersible tablets, Artemether, Lumefantrine, Sodium starch glycolate, crospovidone, Direct Compression.

INTRODUCTION

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(1).

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(2)

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 super disintegrants like cross-linked carboxymethyl cellulose (croscarmellose), sodium starch glycolate (primogel, explotab), polyvinyl pyrollidone (polyplasdone) etc, which provide instantaneous disintegration of tablet(3)

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(4).

Advantages of orally disintegrating drug delivery system(3,5)

- 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 therapy intervention.
- Achieve increased bioavailability/rapid absorption through pregastric absorption of drugs from mouth, pharynx and oesophagus as saliva passes down.
- Convenient for administration and patient compliance for disabled, bedridden patients and for travellers and busy people, who do not always have access to water.

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*(6).

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 during blood 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.(7)

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.

Preparation of co-processed superdisintegrants(8)

The co-processed super disintegrants were prepared by the solvent evaporation method. A blend of crospovidone and sodium starch glycolate (in the ratio of 1:1, 1:2 & 1:3) was added to 10 ml of ethanol. The contents of the beaker (250 ml capacity) were mixed thoroughly and stirring was continued till most of the ethanol evaporated. The wet coherent mass was granulated through no 44 sieves. The wet granules were dried in a hot air oven at 60 ^{O}C for 20 minutes. The dried granules were sifted through no 44 sieves and stored in an airtight container till further use.

Table No 1: Ratio of co-processed disintegrants

Code	Crospovidone+ Sodium starch glycolate	Sodium starch glycolate+ Crospovidone
CS1	1:1	-
CS2	1:2	1:2
CS3	1:3	1:3

Preparation of dispersible tablets by direct compression method(9)

Artemether and Lumefantrine combination Dispersible tablets were prepared by direct compression method by using co-processed superdisintegrants like crospovidone, sodium starch glycolate. croscarmellose sodium as a Disintegrant, hypermellose as a densifier, polysorbate 80as a suspending agent, mannitol, microcrystalline cellulose as a diluent, sodium saccharin as a sweetening agent, mint as a flavour, Magnesium Stearate and Talc used as a lubricant and glidant. All the ingredients (except granular directly compressible excipients) were passed through # 60-mesh separately. Then the ingredients were weighed and mixed in geometrical order after sufficient mixing of the drug as well as other components and compressed into tablets of 400 mg using 14 mm circular, flat, bevel-edged tablets with break line on one side and plain on the other side punch on 12 stations rotary tablet machine.

Table No 2: Formulation Chart

FORMULA CODE	F1 (CPO)	F2 (1:1)	F3 (1:2)	F4 (1:3)	F5 (1:1)	F6 (1:2)	F7 (1:3)	F8 (1:2)	F9 (1:3)	F10 (1:2)	F11 (1:3)
ARTEMETHER	20	20	20	20	20	20	20	20	20	20	20
LUMEFANTRINE	120	120	120	120	120	120	120	120	120	120	120
CO-PROCESSED SUPERDISINTEGRANTS	-	25	25	25	25	25	25	25	25	25	25
MCC	75	75	75	75	75	75	75	75	75	75	75
CROSSCARMELLOSE SODIUM	30	30	30	30	30	30	30	30	30	30	30
MANNITOL	120	95	95	95	95	95	95	95	95	95	95
SODIUM SACCHARIN	8	8	8	8	8	8	8	8	8	8	8
FLAVOUR	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	.5
MAGNESIUM STEARATE	7.5	7.5	7.5	7.5.	7.5	7.5	7.5	7.5	7.5	7.5	7.5
TWEEN 80	3	3	3	3	3	3	3	3	3	3	3
HYPERMELLOSE	6	6	6	6	6	6	6	6	6	6	6
TALC	8	8	8	8	8	8	8	8	8	8	8
TOTAL WEIGHT	400	400	400	400	400	400	400	400	400	400	400

Analytical Method used in the determination of Artemether and Lumefantrine combination.

Melting point: The melting point was determined by the open capillary method.

Identification of pure drug: Identification of Artemether and Lumefantrine was carried out by Infra-Red Absorption Spectrophotometer Separately.

Standard calibration curve of Artemether in 0.5% of SLS phosphate buffer.

Artemether (100 mg) was dissolved in a small amount of 0.5% of SLS phosphate buffer and volume was made up to 100 ml using the same which is called the stock-I solution. 5 ml of the above solution is diluted to 50 ml in another volumetric flask which is called a Stock-II solution. From this stock-II solution, serial dilutions were made by pipetting out 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml to obtain solutions of the drug in the concentration ranging from 5, 10, 15, 20, 25 µg/ml respectively. The absorbance of the solutions was measured at 211 nm using a UV-visible spectrophotometer. A graph of concentration Vs absorbance was plotted.

Standard calibration curve of Lumefantrine in 0.1 N HCl Containing 0.5% Tween 80.

Lumefantrine (100 mg) was dissolved in a small amount of 0.1 N HCl Containing 0.5% Tween 80 and volume was made up to 100 ml using the same which is called a stock-I solution. 5 ml of the above solution is diluted to 50 ml in another volumetric flask which is called a Stock-II solution. From this stock-II solution, serial dilutions were made by pipetting out 0.5 ml, 1 ml, 1.5 ml, 2 ml, and 2.5 ml to obtain solutions of the drug in the concentration ranging from 5, 10, 15, 20, 25 µg/ml respectively. The absorbance of the solutions was measured at 342 nm using a UV-visible spectrophotometer. A graph of concentration Vs absorbance was plotted.

Compatibility study

A weighed amount of drug (3 mg) was mixed with 100 mg of potassium bromide (dried at 40-50 ^{O}C). The mixture was taken and compressed under 10-ton pressure in a hydraulic press to form a transparent pellet. The pellet was scanned by an IR spectrophotometer. A similar procedure is followed for all relevant excipients used.

RESULTS AND DISCUSSION

Melting point

The melting point of Artemether and Lumefantrine was determined by capillary method melting point was found to be 87 ºC and 127 ºC respectively.

Solubility studies

Artemether is soluble in ethanol, methanol and 0.5% Sodium Lauryl Sulphate (SLS) phosphate buffer solution, different basic phosphate buffers of pH 6.8, 7.2, 7.4,7.8. But it was found to be practically insoluble in water.

Lumefantrine is soluble in organic solvents and 0.1 N HCl containing Tween 80, different buffer of pH 6.8, 4.2, 1.2. But it was found to be practically insoluble in water.

Compatibility study of drug with polymers

The physical mixture of drug and polymer was characterized by FTIR spectral analysis for any physical as well as chemical alteration of the drug characteristics. From the results, it was concluded that there was no interference of the functional group as the principle peaks of the Artemether and Lumefantrine were found to be unaltered in the drug-polymer physical mixtures, indicating they were compatible chemically.

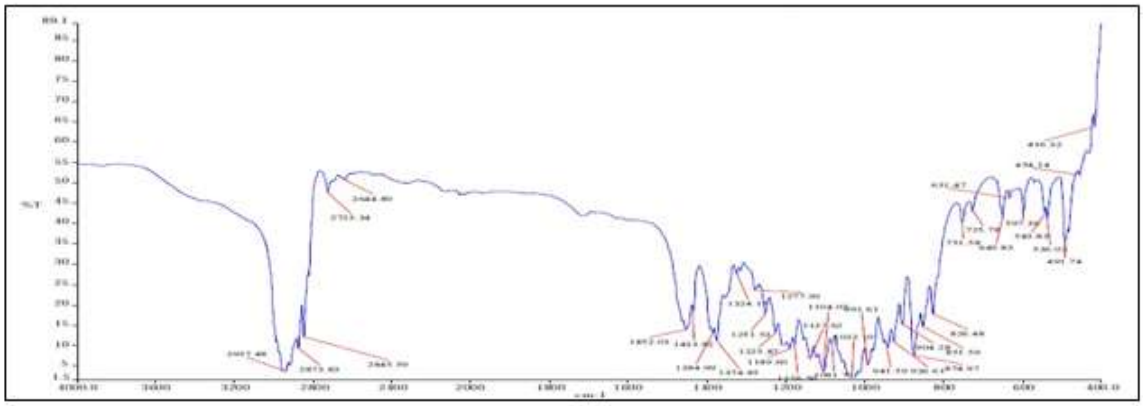

Figure 1: FTIR characteristic peak of Artemether

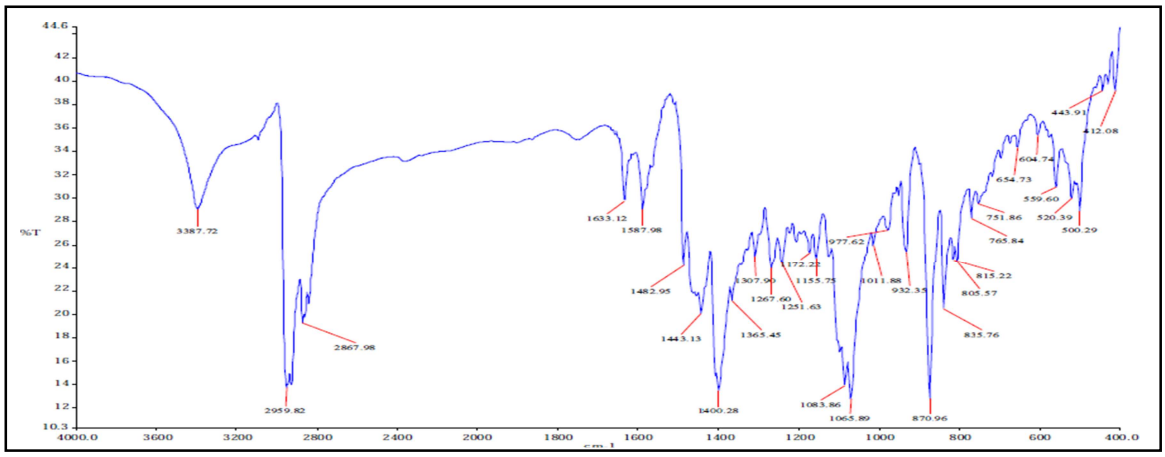

Figure 2: FTIR characteristic peak of Lumefantrine

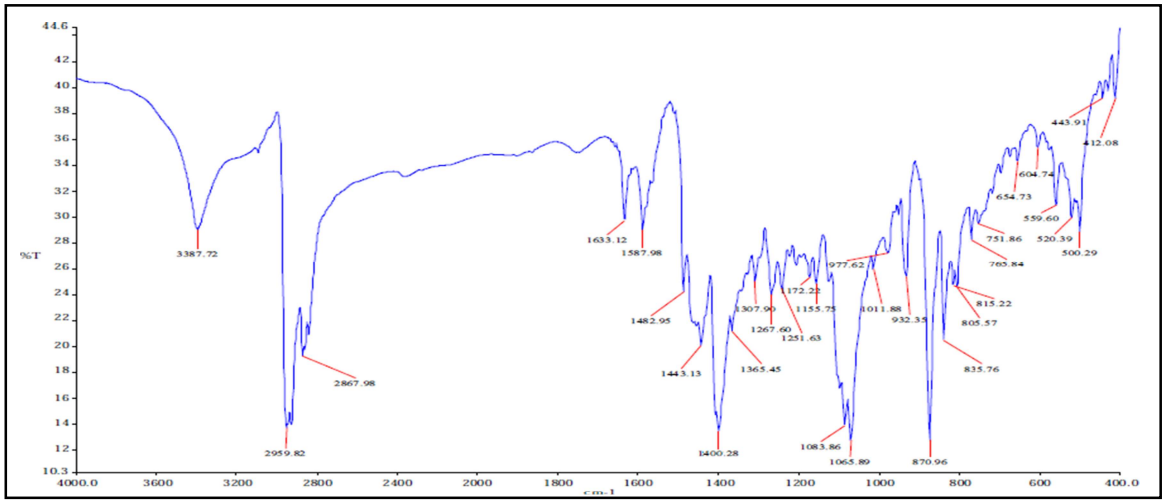

Figure 3: FTIR spectrum with polymers

Standard graph of Artemether

λ_{max} of Artemether was found to be 211 nm as it shows maximum absorbance in this wavelength.

Determination of λ_{max} and preparation of standard curve

The solvent medium was selected based on solubility and it was found that the solubility of Artemether was highest and freely in 0.5% of SLS phosphate buffer. The standard stock solution was prepared as per the method described in methodology and scanned by UV spectrophotometer as per methodology. The λ_{max} was found to be 211 nm against 0.5% SLS phosphate buffer as blank.The standard curve and data were obtained by the procedure described in the methodology. The linear plot between concentrations versus absorbance showed that Beer-Lambert's law was obeyed in the concentration range of 5-25 µg/ml.

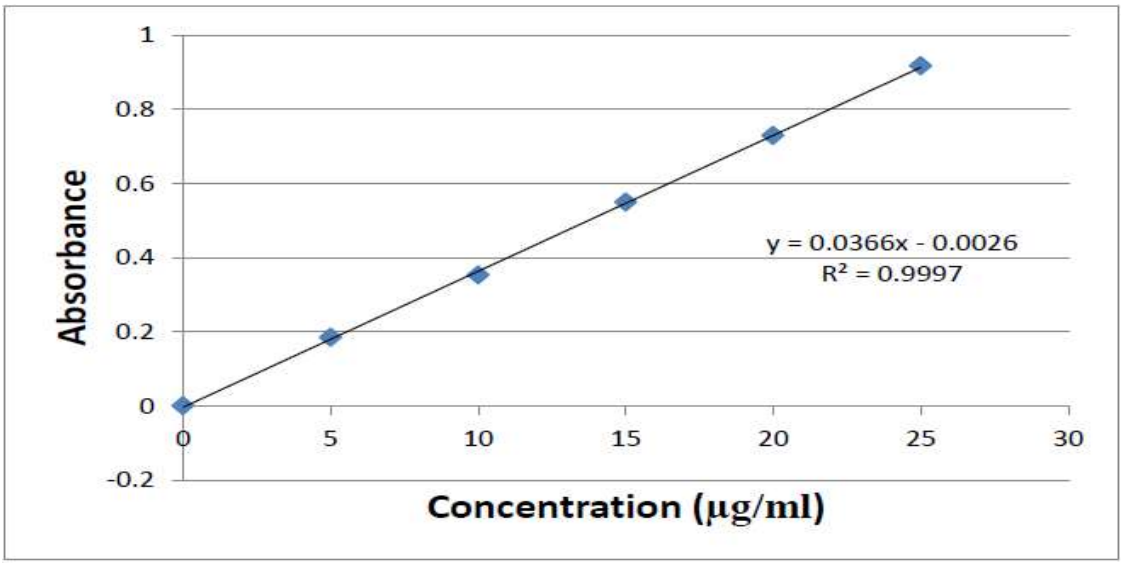

Figure 4: Standard graph of Artemether

λ_{max} of Lumefantrine was found to be 342 nm as it shows maximum absorbance in this wavelength.

Determination of λ_{max} and preparation of standard curve

The solvent medium was selected based on solubility and it was found that the solubility of Lumefantrine was highest and freely in 0.1N HCl Containing 0.5% Tween 80. The standard stock solution was prepared as per the method described in methodology and scanned by UV spectrophotometer as per methodology. The λ_{max} was found to be 342 nm against 0.1N HCl Containing 0.5% Tween 80 as blank.

The standard curve and data were obtained by the procedure described in the methodology. The results were shown in table 25 and figure 8. The linear plot between concentrations versus absorbance showed that Beer-Lambert's law was obeyed in the concentration range of 5-25 µg/ml.

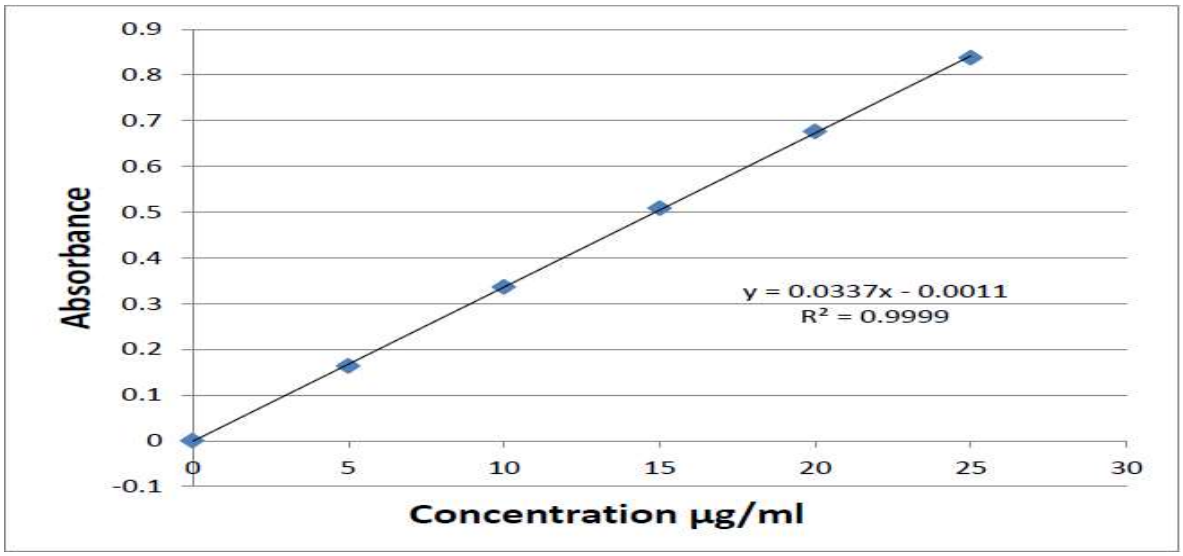

Figure 5: Standard graph of Lumefantrine

Pre-formulation studies

For each type of formulation blends of API and excipients were prepared and evaluated for various parameters as explained earlier. Bulk density was found in the range of 0.476-0.588 g/cm^3 and the tapped density between 0.555-0.714 g/cm^3. Using the above two density data, Carr's compressibility index were calculated. The compressibility index was found between 14.9-21.02% and the compressibility and flowability data indicated good flow properties of all powder blends. The better flow property of all powder blends was also evident from the angle of repose. The angle of repose was in the range of 24.12°-29.56°. The angle of repose below 30º indicates good flow property. In the present study, all powder blends showed good flow property.

Table No 4: Pre-formulation studies results

Code	Bulk density g/cc	Tapped density g/cc	Carr's index%	Hausner's ratio	Angle of repose(°)
F1	0.526±0.094	0.666±0.120	21.02±0.03	1.26	29.56±0.04
F2	0.526±0.101	0.666±0.034	21.02±0.094	1.26	29.19±0.067
F3	0.588±0.074	0.714±0.069	17.64±0.065	1.21	27.89±0.051
F4	0.555±0.089	0.666±0.091	16.6±0.074	1.2	26.21±0.079
F5	0.476±0.093	0.588±0.113	19.04±0.093	1.23	27.97±0.084
F6	0.476±0.112	0.555±0.108	14.23±0.034	1.16	27.61±0.099
F7	0.5±0.107	0.588±0.07	14.9±0.107	1.17	25.52±0.021
F8	0.526±0.099	0.666±0.074	21.02±0.099	1.26	25.86±0.044
F9	0.5±0.094	0.625±0.043	20.0±0.102	1.25	24.12±0.042
F10	0.5260.067	0.666±0.021	20.02±0.074	1.26	27.61±0.042
F11	0.5±0.086	0.625±0.09	20±0.065	1.25	25.86±0.042

Formulation of dispersible tablets of Artemether and Lumefantrine

Eleven formulations of dispersible tablets containing Artemether and Lumefantrine combination were prepared according to the procedure described in the methodology. The formulation procedures have been selected from various research articles and journals. Crospovidone and sodium starch glycolate used as super disintegrants, cross carmellose sodium used as a disintegrant, mannitol and microcrystalline cellulose used as diluents, Hypermellose used as a densifier, Tween 80 used as an emulsifying agent, saccharin sodium, mint used as sweetening agent and flavour.

Tabletting: The uniform blends of tablet composition were directly compressed by keeping the tablet press setting constant across all formulations. Proper lubrication of powder blends was essential for ease of ejection of compressed tablets as well for the free movement of lower punch during compression cycle to eliminate any possible influence of these factors on the study.

Table no 5: Formulation Chart

FORMULA CODE	F1 (CPO)	F2 (1:1)	F3 (1:2)	F4 (1:3)	F5 (1:1)	F6 (1:2)	F7 (1:3)	F8 (1:2)	F9 (1:3)	F10 (1:2)	F11 (1:3)
ARTEMETHER	20	20	20	20	20	20	20	20	20	20	20
LUMEFANTRINE	120	120	120	120	120	120	120	120	120	120	120
CO-PROCESSED SUPERDISINTEGRANTS	-	25	25	25	25	25	25	25	25	25	25
MCC	75	75	75	75	75	75	75	75	75	75	75
CROSSCARMELLOSE SODIUM	30	30	30	30	30	30	30	30	30	30	30
MANNITOL	120	95	95	95	95	95	95	95	95	95	95
SODIUM SACCHARIN	8	8	8	8	8	8	8	8	8	8	8
FLAVOUR	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	.5
MAGNESIUM STEARATE	7.5	7.5	7.5	7.5.	7.5	7.5	7.5	7.5	7.5	7.5	7.5
TWEEN 80	3	3	3	3	3	3	3	3	3	3	3
HYPERMELLOSE	6	6	6	6	6	6	6	6	6	6	6
TALC	8	8	8	8	8	8	8	8	8	8	8
TOTAL WEIGHT	400	400	400	400	400	400	400	400	400	400	400

CONCLUSION

It can be concluded from the present work that co-processed superdisintegrants of crospovidone and sodium starch glycolate are superior to the physical mixture of crospovidone and sodium starch glycolate used in Artemether and Lumefantrine dispersible tablets by direct compression method.

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