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Original Research Article

FORMULATION AND EVALUATION OF ANTIMALERIAL AND ANTIBIOTICS AS COMBINATION THERAPIES

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Abstract: Since malaria is an illness that may rapidly progress to severe disease and even death, early diagnosis and prompt treatment of acute malaria episodes is an important strategy to reduce morbidity and mortality. The first and most important role of diagnosis is in patient management. Currently there is several medicines are available in the market and containing individual drugs. The major challenge in the malaria to provide or prescribe required dose to cure it in due course of time. The major part covered here to develop the combination therapy required to treat malaria to avoid over or low dose during the treatment. The main drug used in the treatment is Chloroquine and Azithromycin to cure in shortest period of time.

In present invention, the development of fix dose combination of Azithromycin and Chloroquine required treating malaria as most effective treatment. Based on overall literature search and studies, it was found that Azithromycin 250mg and Chloroquine 200mg are most suitable strength and combination to be used to trite the malaria. The objective of the present study was to formulate suspension of Azithromycin dihydrate (AZT) and Chloroquine (CQ)as fix dose combination useful to treat Malaria. Individually, Azithromycin and Chloroquine tablets are available in the market to treat malaria. However, there is no fix treatment dose are given during treatment. The present study is to develop safest and effective fix dose combination of Azithromycin and Chloroquine tablets.

Kev words: Azithromycin. Chloroquine. Fix dose combination. Malaria. Disintegration time:

Introduction: Despite of tremendous innovations in drug delivery, the oral route remains the preferred route for administration of therapeutic agents because of accurate dosage, low cost therapy, self-medication, noninvasive method and ease of administration leading to high level of patient compliance. Pediatric and geriatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control [1].The development of Azithromycin 250mg and

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Chloroquine 200mg Tablets was initiated based on general pharmaceutical techniques and drug substance characteristics. The development objective was to prepare a prototype formulation comparable in performance with individual available products in the markets. The robustness of the formulation and process was established by preparing several experimental batches at the laboratory scale.

Materials and method

Materials: Azithromycin was obtained from Ciron Pharma Pvt. Ltd., Mumbai; Chloroquine was obtained from IPCA Laboratory, Sodium Lauryl Sulphate, Povidone K 90, Crospovidone CLF, Crospovidone CLF are obtained from BASF, Microcrystalline cellulose obtained from FMC and Talc was obtained from Luzenac and film coating material was obtained from Colorcon.

Methods: Azithromycin is having poor flow properties hence wet granulation approach was adopted to develop the formulation. The sodium lauryl Sulphate was used to get solubilize the Chloroquine as due to its low solubility; optimum concentration for the same was optimized. Microcrystalline cellulose used 11% of the total drug product composition. The particle size distribution, particle morphology, aspect ratio, bulk density and flowability of different grades have the potential to affect drug product content uniformity. Overall the selections of all excipients are based on the need of drug development in combination therapy.

Half quantity of PVPK90 was dissolved in purified water till clear solution obtained. Azithromycin, Kolliphore SLS fine, crospovidone CLF and remaining quantity of PVPK90 through were sifted through 40 mesh and loaded 3L RMG and dry mixed for 10 minutes at 200 RLM. The dry mixed material were granulated using PVPK90 solution till desired consistency of granules obtained. Wet granules further dried in Restch dryer till LOD achieved. Dried granules further milled to suitable screen and loaded in bin blender. Chloroquine, Avicel PH 112, aerosil, and crospovidone CLF through were sifted through # 40 and loaded in bin blender. Dried granules and extra granular materials were blended for 10 minutes to have uniform mixing. Talc was sifted through #40 mesh and lubricated for 5 minutes.

Table 1 Wet granulation optimization

		F1	F2	F3
Sr. No	Ingredients	Mg/tab		
1	Azithromycin	250.0	250.0	250.0
3	Sodium Lauryl Sulphate (Kolliphore SLS fine)	5	7.5	10.0
4	Povidone K 90	40.0	40.0	40.0
5	Crospovidone CLF	20.0	20.0	20.0
6	Povidone K 90	24.0	24.0	24.0
7	Purified water	QS	QS	QS

A granule prepared by different quantity of purified water was milled through 2.0 mm multimill screen at medium speed.

Table 2Extra-granular Part optimization

		F1	F2	F3
Sr. No	Ingredients	Mg/tab		
8	Chloroquine	200.0	200.0	200.0
9	Silica, Colloidal anhydrous	4.0	4.0	4.0
10	Crospovidone CLF	22.0	22.0	22.0
11	Microcrystalline cellulose	60.0	70.0	80.0
12	Talc	10.0	10.0	10.0
	Film coating			
13	Opadry II Brown	20.0	20.0	20.0
14	Purified Water	QS	QS	QS
	Total	655.0	662.5	680.0

Evaluation of pre compression parameters

Bulk and Tapped density: Before final compression of tablets, powdered mixture was subjected to pre compression parameters such as bulk density, tapped density, angle of repose,

powder compressibility and Hausner ratio. All the experiments were done in triplicates and expressed as mean± SD.

Bulk Density: Bulk density was determined by measuring the volume of the predetermined or preweighed mass of the powder blend according to the protocol described [6].

Bulk Density (Db) = (M) / (Vo) (2)

Where,

M = Mass or weight of the powder blend

Vo = Apparent volume of the powder blend into the cylinder

Tapped Density: Tapped density was achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder was mechanically tapped and volume readings were taken until little further volume change was observed. The mechanical tapping was achieved by raising the cylinder and allowing it to drop under its own weight from a specified distance

Tapped density (Dt) = (M) / (V_f) (3)

Where,

M = Mass or weight of the powder blend. V_f = Final volume of the powder blend into the cylinder.

Carr's Index or Compressibility Index (I)

This was calculated by the formula and expressed as percentage (%)

I = Dt -Db / Dt ×100% (4)

Where

Db = Bulk density,Dt = Tapped density.

Hausner Ratio

Hausner ratio is an indirect index of ease of powder flow. It is calculated by the following formula-

Hausner Ratio = D_t/D_b (5)

Where,Db = Bulk density,Dt = Tapped density.

Evaluation of post compression

Appearance: The general appearance of tablet is its visual identity and all over elegance, shape, color, surface textures. These all parameters are essential for consumer acceptance. Tablets have smooth, clean surface, round concave shaped, white color tablet with pleasant taste.

Thickness: The thickness of the tablets was determined by using vernier calipers. Randomly 10 tablets selected and were used for determination of thickness that expressed in mean± SD and unit is mm.

Weight variation: The weight variation test is carried out in order to ensure uniformity in the weight of tablets in a batch. The total weight of 20 tablets randomly from whole batch was determined and the average was calculated. The individual weights of the tablets were also determined accurately and the weight variation was calculated.

Friability test: Friability is the loss of weight of tablet in the container due to removal of fine particles from the surface during transportation or handling. Roche friabilator was employed for finding the friability of the tablets. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Roche friabilator is rotated at 25rpm for 4 minutes for 100rounds. The tablets were dedusted and weighed again. The percentage weight loss was calculated using the formula.

$$F = \frac{W_0 - W_1}{W_0} \times 100$$

Where, F = Percentage friability

W_0 = Initial weight (Before test)

W_1 = Final weight (After test)

In Vitro Disintegration test: The USP device to rest disintegration was six glass tubes that are 3 long, open at the top, and held against 10 screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of distilled water at 37± 0.5^{o}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker[9, 10].

Drug content: 10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media 0.1N HCl. Volume of the solution made up to 100ml by that media.

Solution was filtered and diluted 100times and analyzed spectrophotometrically and further calculation carried out to determine drug content in one tablet.

In vitro dissolution studies: In Vitro release studies of azithromycin and chloroquine from different formulations were performed according to USP XVIII apparatus II, paddle method (Dissolution test apparatus-TDT-06T, Electrolab, Mumbai, India). Paddle speed was maintained at 50 rpm and 900 ml of 0.1N HCl was used as the dissolution medium. Samples (10 ml) were collected at predetermined time intervals (5, 10, 15, 30 and 45 min) and replaced with equal volume of fresh medium, filtered through a 0.45µm filter and analyzed with a UV-visible spectrophotometer (Shimadzu, Japan) at λ= 254 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved [11].

Results and Discussion:

Flow properties of granules: The preformulation study of the powder blend shown that it has low Hausner's ratio(< 1.3), compressibility index (< 17.75 %), angle of repose (<30°) values indicate a fairly good flowability of powder mixture (**Table 3**). As the tablet powder posses free flowing properties so tablets produced of uniform weight.

Table 3: Flow properties of granules

Batch No.	Bulk density (g/cc) ±SD	Tapped density (g/cc) ±SD,	Angle of Repose(θ) (g/cc) ±SD	Carr's Index (%) ±SD	Hausner's Ratio(%) ±SD
F1	0.49±0.007	0.62±0.002	29.45±1.43	15.08±1.1	1.19±0.002
F2	0.52±0.005	0.60±0.004	29.13±1.53	14.88±1.49	1.15±0.005
F3	0.51±0.001	0.63±0.001	25.46±0.89	10.53±1.32	1.11±0.006

n=3

From the results of flow properties of the all batches, it is concluded that all batches had good flow property.

The powder blend was compressed using ten station compression machine. Tablets prepared by using above mentioned formula have found to be good without any chipping, capping and sticking.Various physical parameters like thickness, hardness, weight variation, friability, hardness, disintegration time were measured to evaluate tablets.

All batches passes weight variation test (less than 7.5% Weight variation). Thickness of tablet was found variation less than 5%. Friability of F1 to F3 batches was found less than 0.5 %. **(Table 4)**

Table 4: Post Compression parameters

Batch No.	Thickness ( )	Hardness ()	Weight variation (mg)	Friability (%)
F1	5.46± 0.014	122±0.56	653±5	0.301
F2	5.50±0.116	127±0.44	665±5	0.243
F3	5.51±0.114	135±0.100	680±5	0.108

Table 5: Post Compression Evaluation

Batch No.	Disintegration Time (sec)	% Drug content	
		Azithromycin	Chlororoquine
F1	10± 0.15	99.0	100.0
F2	10±0.12	99.0	101.0
F3	08±0.01	98.9	99.9

Table 6: Drug release

Time points	Azithromycin			Chloroquine		
5	33	41	50	39	47	48
10	50	65	77	68	74	78
15	74	82	91	89	87	93
20	84	91	96	98	94	100
30	92	96	97	100	96	102
45	92	97	97	99	96	101

Fig 1 *Invitro* dissolution of azithromycin batches F1 to F3

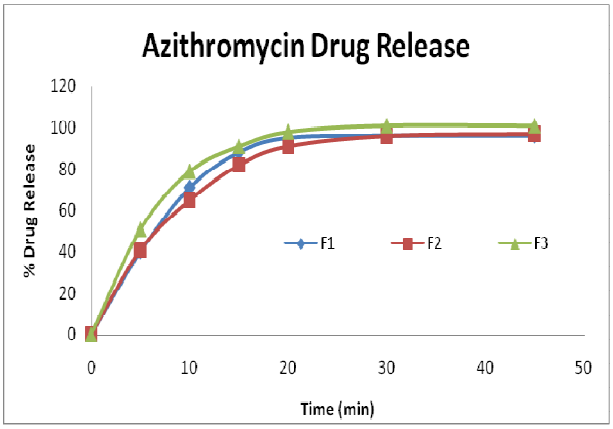
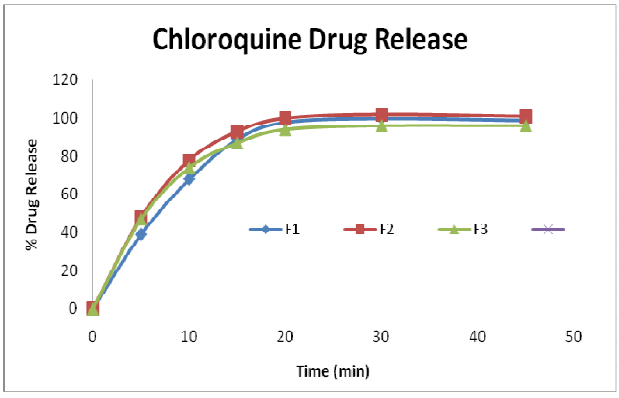


Fig 2 *In vitro* drug release of Chloroquine batches F1 to F3



Stability study: Three months stability study at ambient temperature and relativehumidity (30 °C / 65% RH) of formulation F3 revealed that theformulation was stable and there were no significant changesobserved for hardness, drug content and disintegration time. Hence, the results of stability studies reveal that the developed formulation has good stability.

Conclusion: All formulations showed good disintegration time, apart from fulfilling all compendia and non compendial specifications. During development of Azithroycin and Chloroquine tablets, Critical excipients studied to check the impact on optimum formulation. All the studies and based on the range studies of formulation variable are found to be satisfactory. Physical parameters of batches performed with different concentration are found to be sastifactory. Dissolution results of batches taken with different variant are also found to be satisfactory. Batch charged on stability was found to be satisfactory and no significant degradation were observed.

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