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Formulation and Evaluation of Mouth Dissolving Tablets of Azithromycin Dihydrate and Chloroquine by Melt Granulation

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Abstract: The objective of the present study was to formulate mouth dissolving tablets using PEG 6000 by melt granulation of azithromycin and chloroquine for combination therapy of antimalerial-Antibiotics. Azithromycin is floppy in nature and having very bitter taste hence PEG 6000 was selected to mask the bitter taste and generate granules. In the present study, melt granulation technique was selected. The prepared fast disintegrating tablets were evaluated for weight variation, content uniformity, hardness, disintegration time, wetting time and friability of tablets. Wetting time of formulations containing 100 PEG was least and tablets showed fastest disintegration. All the tablets had acceptable hardness and friability of all formulations was less than 1%, weight variation and drug content were within official limit. Amongst all formulations, formulation F2 prepared showed least disintegrating time of 20 sec and faster dissolution. On the basis of these results, mouth dissolving tablets of azithromycin and chloroquine by melt granulation using PEG 6000 may be considered as a promising alternative to conventional tablets with improved patient compliance.
Keywords: Azithromycin, Chloroquine, Mouth dissolving tablets, 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, non invasive 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. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. ODTs are solid dosage form that dissolves or disintegrates rapidly in oral cavity, resulting in solution or suspension without the need of water [1]. ODT can be prepared by various methods such as freeze drying, sublimation of volatile salts, addition of super disintegrant. The problem of certain ODT is their low hardness and high friability. This work describes a new approach to prepare ODT with sufficient mechanical integrity, involving the use of PEG 6000 by melt granulation technique. PEG 6000 is helping to mask the bitter taste of both API and give pleasant mouth feel.

Azithromycin and Chloroquine are used to treat Plasmodium falciparum resistance. It is challenge to mask bitter taste of azithromycin and chloroquine. Prepare orally dispersible tablets with acceptable taste. In the present study the melt granulation techniques was adopted to manufacture the ODT tablets, since it is very simple and do not require any sophisticated equipments. The melt granulation represents the simplest and most cost effective tablet manufacturing technique which is useful to coat API and mask their bitter taste. This technique has been applied to prepare ODT formulation because of the availability of improved excipients

especially super disintegrants like cross carmalose sodium, directly compressible diluents, sweeteners and flavoring agents. The advantage using PEG 6000 is does not require any lubricants and binding agents separately.

Materials and method

Materials

Azithromycin was obtained from Ciron Pharma Pvt. Ltd., Mumbai; Chloroquine was obtained from IPCA Laboratory, India. Sucralose and Banana flavor was obtained from Kawarlal chemical Pvt. Ltd. Mannitol and Cross carmallose was obtained from Signet Chemical Corporation, Mumbai. Aerosil 200 was obtained from Evonik Degussa Mumbai.

Methods

Azithromycin and Chloroquine orally disintegrating tablets were prepared by melt granulation method. Compositions of various formulations are shown in Table 1. The orally dispersible tablet of Azithromycin and Chloroquine were prepared using polyethylene glycol 6000 as coating agents , Pearlitol 200SD used as diluents, Banana flavor used as flavouring agent, sucralose used as sweetners., Croscarmellose Sodium used as disintegrating agents.

Azithromycin and Chloroquine were sifted through 40 mesh and loaded 3L RMG. Both API were mixed for 10 minutes at 500RPM. PEG 6000 was added in 500 ml glass beaker and was heated at 40°c until it was completely melt. Melted PEG 6000 was added in dry mixed azithromycin and chloroquine mixture at 200RPM of impeller in 5 minutes followed by kneading for 5 more minutes at 200RPM of impeller and 1400 RPM of chopper. Granulated material kept for 1 hour in room temperature to get solidifies PEG 6000. Formulation optimization was done using different quantity of PEG 6000 to get desired consistency of granules with acceptable taste, refer table one was showing different quantity of PEG 6000 during the granulation.

Table 1 Optimization of PEG 6000 quantity.

Ingredients	F1	F 2	F 3	F 4	F5	F6
Azithromycin	250	250	250	250	250	250
Chloroquine	150	150	150	150	150	150
PEG 6000	50	100	150	175	200	225
Total	450	500	550	575	600	625

A granule prepared by melt granulation was milled through 2.0 mm multimill screen at medium speed. Crosscarmalose sodium, mannitol, aerosil pharma 200, banana flavour and sucralose were sifted through 40 mesh manually. Further milled granules and sifted material were blended in 5L blender for 15 minutes at 10 RPM.

Table 2 Blending:

Ingredients	F 1	F 2	F 3	F 4	F5	F6
Azi-Chlo and PEG 6000 granules	450	500	550	575	600	625
Crosscarmalose sodium	50	50	50	50	50	50
Mannitol	200	200	200	200	200	200
Aerosil	20	20	20	20	20	20
Banana Flavour	20	20	20	20	20	20
Sucralose	20	20	20	20	20	20
Total	760	810	860	885	910	935

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 pre weighed 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 (%)

$$I = Dt - Db / Dt \times 100\% \quad (4)$$

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.

Angle of Repose (θ)

The determination of angle of repose of powder blend was carried out by employing fixed funnel method

$\tan \theta = H/R$, (6)

Where, H = height of the pile, R = radius of the pile

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].

Disintegration in Oral Cavity

The time required for complete disintegration of tablet in oral cavity was obtained from six healthy volunteers, who were given tablets from all the formulations [11, 12].

Wetting Time

The wetting time of the tablets was measured using a simple procedure. Five circular tissue papers of 10 cm diameter were placed in a petri dish containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required for develop blue color due to amaranth water soluble dye on the upper surface of the tablets was noted as the wetting time.

Water Absorption Ratio (R)

The weight of the tablet prior to placement in the Petri dish was noted (W_b) utilizing a Shimadzu digital balance. The wetted tablet was removed and reweighed (W_a). Water absorption ratio, R, was then determined according to the following equation. Where W_b and W_a were tablet weights before and after water absorption, respectively [14].

$$R = \frac{(W_b - W_a)}{W_a} \times 100$$

Where, R = Water absorption ratio
W_b = Weight of tablet before water absorption
W_a = Weight of tablet after water absorption

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 0.45 μm 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 [13].

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 flow ability 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	0.50±0.002	0.65±0.001	29.25±1.43	15.08±1.1	1.30±0.003
F2	0.53±0.008	0.63±0.003	28.16±1.53	15.88±1.49	1.18±0.004
F3	0.52±0.007	0.60±0.001	26.46±0.88	13.53±1.32	1.16±0.002
F4	0.51±0.005	0.62±0.002	29.08±1.01	17.74±1.11	1.21±0.001
F5	0.53±0.006	0.63±0.004	29.88±1.25	15.87±1.56	1.18±0.001
F6	0.55±0.004	0.64±0.002	28.40±1.56	15.86±1.44	1.16±0.003

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 F6 batches was found less than 0.5 %. (Table 4)

Table 4: Post Compression parameters

Batch No.	Thickness	Hardness	Weight variation (mg)	Friability (%)
F1	2.54± 0.014	45±0.199	760 ±5	0.330
F2	2.77±0.116	44±0.122	810±5	0.345
F3	2.99±0.114	45±0.122	860±5	0.455
F4	3.10±0.119	47±0.111	885±5	0.191
F5	3.32±0.110	42±0.156	910±5	0.455
F6	3.61±0.115	44±0.129	935±5	0.256

Table 5: Post Compression Evaluation

Batch No.	Disintegration Time (sec)	Disintegration in oral cavity time (sec)	Average Wetting Time (sec)	Water absorption ratio (%)	% Drug content	
					Azithromycin	Chlororoquine
F1	20± 0.014	45±0.199	18±0.322	76.45±0.033	99.0	100.0
F2	19±0.116	44±0.122	16±0.345	78.52±0.345	99.0	101.0
F3	25±0.114	45±0.122	20±0.351	78.35±0.455	98.9	99.9
F4	30±0.119	47±0.111	19±0.322	83.17±0.191	99.5	97.8
F5	33±0.110	42±0.156	21±0.521	78.92±0.455	97.8	99.5
F6	49±0.115	44±0.129	22±0.365	83.45±0.256	98.2	99.7

As per the pharmacopoeial requirement, formulation of fast disintegrating tablet exhibited disintegration time in ≤ 60 seconds; F1 to F6 batches passes the disintegration time requirement. From the above it is observed that all the prepared formulations exhibited disintegration time less than 60 seconds from F1 to F6 batches. F2 batch exhibited the least disintegration time i.e. 20 seconds and acceptable mouth feel. So from above observation it is concluded that the optimized formulations (Batch F5) contains PEG is sufficient to mask the aizthromycin taste and provide less DT. The results obtained from wetting and disintegration was found to be within the acceptable limits and the criteria for mouth dissolving tablets (Table 5). *In vitro* wetting time was in the range of 16 to 22 s while the *in vitro* disintegration time was 19 to 49 s (Table 5).

Fig 1 and Fig 2 demonstrate dissolution profile of azithromycin and chloroquine respectively form mouth dissolving tablet; more than 80% of drug gets dissolved within 5 min. Since mouth dissolving tablets are expected to dissolve in least possible time

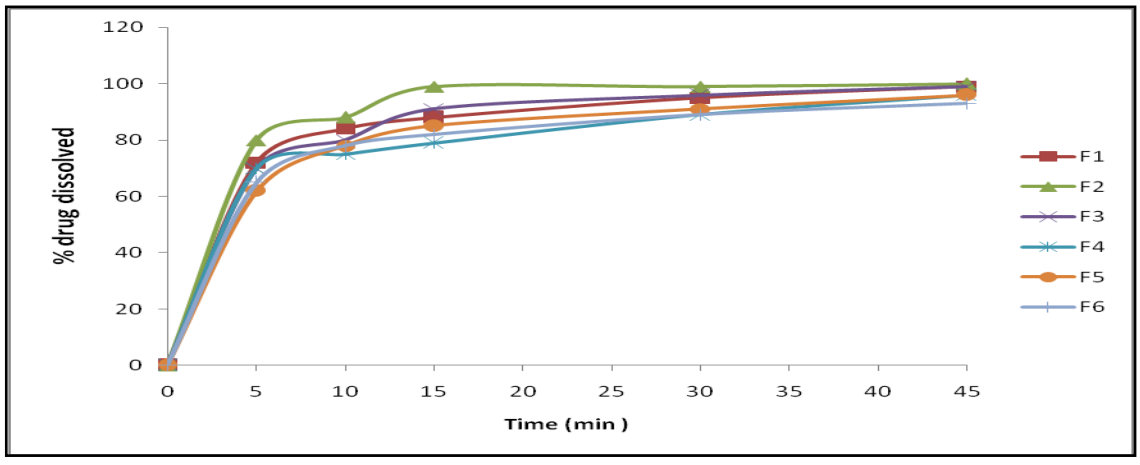

Fig 1 *In vitro* dissolution of azithromycin batches F1 to F6

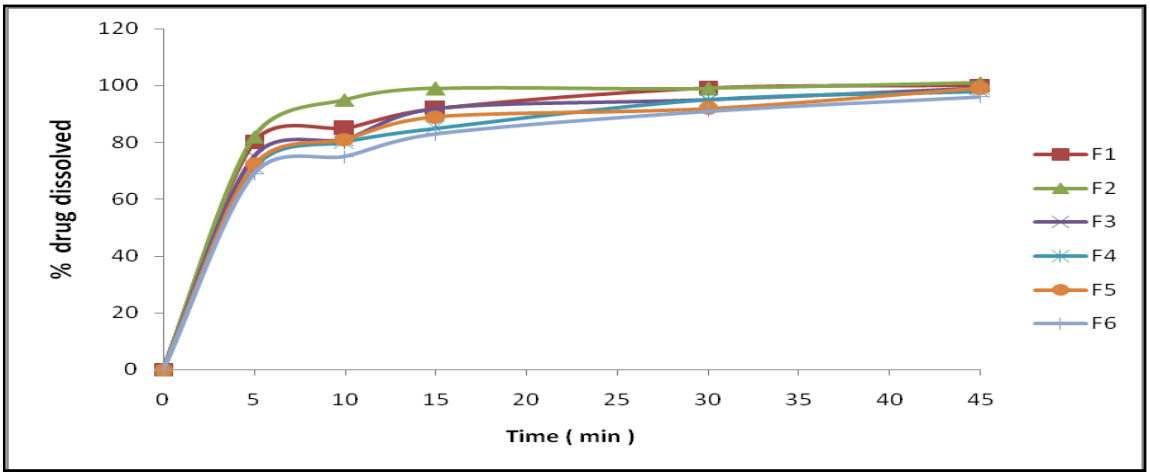

Fig 2 *In vitro* drug release of Chloroquine batches F1 to F6

Conclusion

Stable, effective and pleasant tasting mouth disintegrating tablet, exhibiting an excellent disintegration time and dissolution profile, was formulated using cross carmellose sodium as disintegrating agent containing azithromycin and chloroquine. The formulation was developed with aim to provide a convenient means of taking medication to the patients suffering from malaria. The main purpose was to achieve rapid disintegration and dissolution using a cost effective, industry feasible method involving conventional tabletting facilities. All formulations showed good disintegration time, apart from fulfilling all compendia and non compendial specifications.

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