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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF TASTE MASKED IMMEDIATE RELEASE TABLETS OF AZITHROMYCIN DIHYDRATE AND CHLOROQUINE PHOSPHAT USING β-CYCLODEXTRIN

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Abstract:
The main aim of the present study was to evaluate complexation as an approach for taste masking. For this purpose Azithromycin and Chloroquine with property of bitter taste was selected as a model drug used for combination therapy. Improvement in taste masking capability of cyclodextrin towards Azithromycine was evaluated by formulating a ternary complex. *In vitro* dissolution study was carried out to see the effect of ternary complexation on drug release. Taste perception study was carried out on human volunteers to evaluate the taste masking ability of ternary complexsation. Complexation system showed effective taste masking as compared to binary complex and at the same time showed no limiting effect on the drug release (D.E15min = 90%). The effective taste masking was attributed to the enhanced complexsation of Azithromycin from the characterization studies. In conclusion, the study confirmed that complexsation can be utilized as an alternative approach for effective taste masking.

Keywords: Azithromycin, Chloroquine, Beta Cyclodextrin, ODT, Disintegration time; wetting time and taste masking.

Introduction

The oral route of administration is the most preferred route due to its many advantages like ease of administration, accurate dosage, self-medication, pain avoidance, versatility and patient compliance. Tablets and capsules are the most popular dosage forms.

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.
To solve the above-mentioned problems, pharmaceutical technologists have put in their best efforts to develop a Fast dissolving drug delivery, i.e. Mouth Dissolving Tablet that disintegrates and dissolves rapidly in the saliva, within a few sec without the need of drinking water or chewing. Mouth dissolving tablet usually dissolves in the oral cavity within 15 sec to 3 min. Most of the ODTs include certain super disintegrant and taste masking agents. ODTs and granules are solid dosage form that dissolves or disintegrates rapidly in oral cavity,

resulting in solution or suspension without the need of water [1].
ODTs and granules 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 superdisintegrant. The problem of certain ODT is their low hardness and high friability. This work describes a new approach to prepare ODT granulation technique. Beta cyclodextrin is helping to mask the bitter taste of both API and give pleasant mouth feel.

In present research work, oral dispersible tablet of Azithromycin and Chloroquine is used in formulated using complexation with betacyclodextrin by wet granulation technique. Azithormycin has very bitter test and has half life and its challenging to mask bitter taste of azithromycin in present study. Azithromycin and Chloroquine are used to treat Plasmodium falciparum resistance. It is challenge to mask bitter taste of azithromycin and chloroquine and prepare orally dispersible tablets with acceptable taste. In the present study the RMG granulation techniques was adopted to manufacture the ODT tablets, since it is very simple and do not require any sophisticated equipment's. The conventional granulation represents the simplest and most cost effective tablet manufacturing technique which is useful to mask the bitter taste of API. This technique has been applied to prepare ODT formulation because of the availability of improved excipients especially superdisintegrant like Crosscarmalose sodium, directly compressible diluents, sweeteners and flavoring agents.

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 crosscarmalose was obtained from Signet Chemical Corporation, Mumbai. Aerosil 200 was obtained from Evonik Mumbai and Cyclodextrin was obtained from Gangwal chemicals.

Methods

Azithromycin and Chloroquine orally disintegrating tablets were prepared by wet granulation method. Compositions of various formulations are shown in Table 1. The orally dispersible tablet of Azithromycin and Chloroquine were prepared using cyclodextrin as complexation agent , Perlitol 200SD used as diluents, Banana flavor used as flavoring agent, sucralose used as sweeteners., Crosscarmalose Sodium used as disintegrating agents.

Azithromycin, Chloroquine and Beta-cyclodextrin were sifted through 40 mesh and loaded 3L RMG. Materials purified water in glass beaker. Weighed quantity of purified water was added in dry mixed materials at 200RPM of impeller in 2 minutes followed by kneading for 1 more minutes at 200RPM of impeller and 1400 RPM of chopper. Granulated material passed through 8# mesh. Passed materials were dried at 60 ^{o}C till % LOD was NMT 1 %. Formulation optimization was done using different quantity of betacyclodextrin to mask bitter taste of the Azithromycin, refer table one was showing different quantity of betacyclodextrin during the granulation.

A granule prepared by wet granulation was milled through 2.0mm 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.

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) / (Vf) (3)
Where,
M = Mass or weight of the powder blend
Vf = 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 (%)

were mixed for 10 minutes at 500RPM. Weighed 100 g

$I = Dt - Db / Dt \times 100\%$ (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 = Dt/Db (5)

Where,

Db = Bulk density,

Dt = Tapped density.

Angle of Repose

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

Angle of Repose = tan -1 (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 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 4minutes for 100rounds. The tablets were dedusted and weighed again. The percentage weight loss was calculated using the formula.

$$\% F = \frac{W0 - W1}{W0} \times 100 \quad (7)$$

Here, % F = Percentage friability

W0 = Initial weight (Before test)

W1 = 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± 2oC, 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 10cm diameter were placed in a petridish containing 0.2% w/v solution of amaranth (10ml). One tablet was carefully placed on the surface of the tissue paper. The time required to 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 (Wb) utilizing a Shimadzu digital balance. The wetted tablet was removed and reweighed (Wa). Water absorption ratio, R, was then determined according to the following equation. Where Wb and Wa were tablet weights before and after water absorption, respectively (14).

$$R = \frac{(Wb - Wa)}{Wa} \times 100 \quad (8)$$

Here,

R = Water absorption ratio

Wb = Weight of tablet before water absorption

Wa = Weight of tablet after water absorption

Drug content:

Total 10 tablets were powdered and 100mg drug equivalent powder dissolved in suitable media 0.1N HCl. Volume of the solution made up to 100 ml by that media. Solution wasfiltered and diluted 100 times and analyzed

Table 1 Optimization of β- cyclodextrin 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
β-cyclodextrin	25	50	75	100	150	200
Total	425	450	475	500	550	600

Table 2 Blending:

Ingredients	F 1	F 2	F 3	F 4	F5	F6
Azi-Chlo and Betacyclodextrin granules	425	450	475	500	550	600
Crosscarmalose sodium	50	50	50	50	50	50
Mannitol	200	200	200	200	200	200
Aerosil Pharma 200	20	20	20	20	20	20
Banana Flavour	20	20	20	20	20	20
Sucralose	20	20	20	20	20	20
Total	735	760	785	810	860	910

Table 3: Angle of repose of granules of batch F1 to F6

Batch No.	Bulk density (g/cc) ±SD, n=3	Tapped density (g/cc) ±SD, n=3	Angle of Repose(θ) (g/cc) ±SD, n=3	Carr's Index (%)±SD, n=3	Hausner's Ratio (%)±SD, n=3
F1	0.53±0.002	0.59±0.001	28.25±1.43	15.18±1.1	1.31±0.003
F2	0.54±0.008	0.61±0.003	29.16±1.53	15.58±1.49	1.20±0.004
F3	0.55±0.007	0.60±0.001	28.46±0.88	14.53±1.32	1.18±0.002
F4	0.56±0.005	0.61±0.002	28.08±1.01	16.54±1.11	1.21±0.001
F5	0.55±0.006	0.62±0.004	29.88±1.25	16.87±1.56	1.18±0.001
F6	0.55±0.004	0.62±0.002	29.40±1.56	16.86±1.44	1.16±0.003

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

Table 4: Post Compression parameters

Batch No.	Thickness	Hardness	Weight variation	Friability
F1	2.8± 0.014	40±0.199	735±0.222	0.001±0.025
F2	2.90±0.116	44±0.122	760±0.256	0.241±0.018
F3	3.05±0.114	41±0.122	785±0.014	0.199±0.045
F4	3.10±0.119	49±0.111	810±0.287	0.185±0.110
F5	3.40±0.110	43±0.156	860±0.365	0.248±0.098
F6	3.58±0.115	44±0.129	910±0.458	0.126±0.075

Table 5: Post Compression Evaluation

Batch No.	Average Disintegration Time (sec)	In-vitro disintegration time (sec)	Average Wetting Time (sec)	Water absorption ratio (%)	% drug content	
					Azithro	Chloro
F1	18± 0.014	20±0.122	18±0.322	79.14±0.031	99.5	100.2
F2	15±0.116	22±0.185	16±0.345	77.57±0.314	100	99.2
F3	21±0.114	30±0.196	20±0.351	77.53±0.296	99.9	99.5
F4	22±0.119	35±0.158	19±0.322	78.17±0.121	99.8	100.3
F5	25±0.110	39±0.159	21±0.521	84.22±0.325	100.2	99.9
F6	30±0.115	44±0.192	22±0.365	85.49±0.286	99.8	99.8

Figure 1 In-vitro drug release of Azithromycin batches F1 to F6

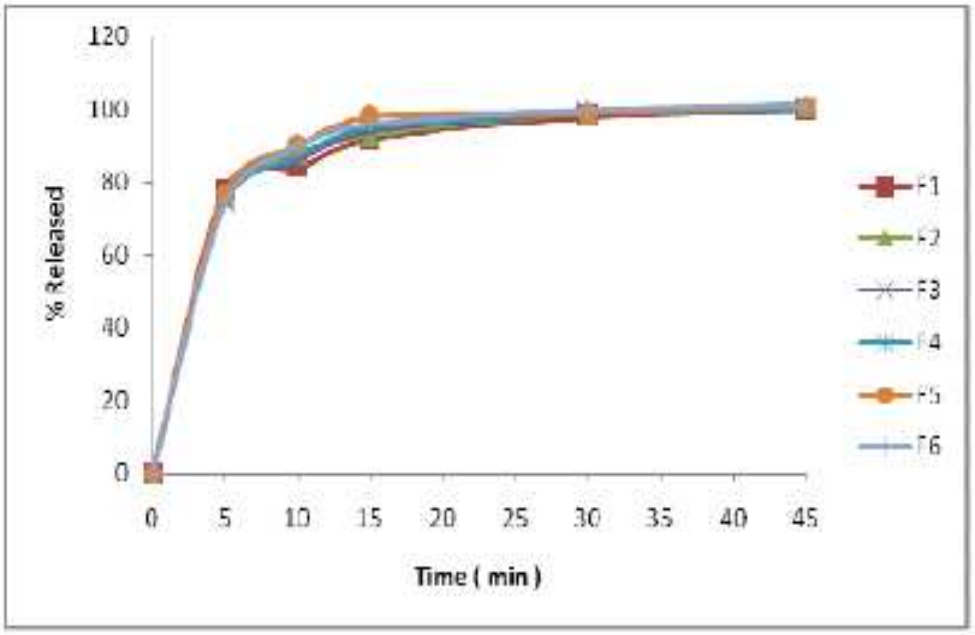
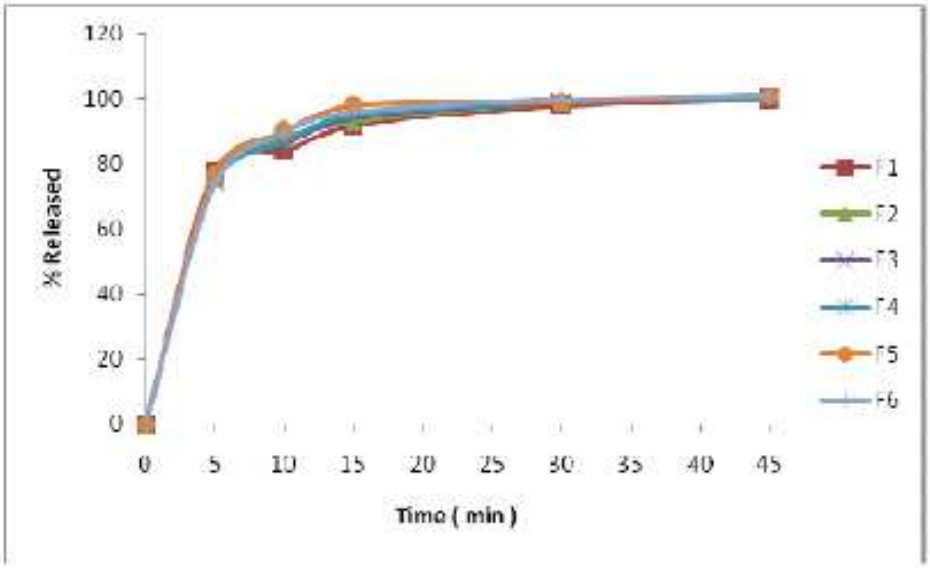


Figure 2: In-vitro drug release of Chloroquine batches F1 to F6



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 _= 254 nm. Drug concentration was calculated from a standard calibration plot and expressed as cumulative % drug dissolved[13].

Stability Study:

The stability of samples was monitored upto 3-month at ambient temperature and relative humidity (30°C/65% RH). Periodically samples were removed andcharacterized for disintegration time, hardness, drug-content and dispersion time.

RESULTS AND DISCUSSION

FLOW PROPERTIES OF GRANULES:

Angle of Repose of Granules: All batches were evaluated for flow property. The results of all the batches were shown in table 3.

Post compression parameters

The powder blend was compressed using 4 station compression machine. Tablets prepared by using 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 the formulations have therefore thought to show the acceptable physical parameters of tablets. As per the pharmacopoeial requirement, formulation of oral 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. F5 batch exhibited the least disintegration time i.e. 25 seconds and acceptable mouths feel. So from above observation it is concluded that the optimized formulations (batch F5) contains betacyclodextrin is sufficient to mask the azithromycin taste with acceptable DT.

Stability study

Three months stability study at ambient temperature and relativehumidity (30 °C / 65% RH) of formulation F5 revealed that tablet formulation was stable and there were no significant changesobserved for hardness, drug content and disintegration time. Hence, the results of stability studies reveal that the developedformulation has good stability.

Conclusion

The study conclusively demonstrated complete taste masking of azithromycin and chloroquine and rapid disintegration and dissolution of ODT. Taste masking and rapid disintegration of tablets formulated in this investigation may possibly help in administration of bitter drugs in a more palatable form without water. Thus, the "patient-friendly dosage form" of bitter drugs, especially for pediatric, geriatric, bedridden, and non-cooperative patients, can be successfully formulated using this technology

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