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Research Article

COMPARATIVE EVALUATION OF FAST DISSOLVING TABLETS USING KYRON T-114 AND INDION- 204 USING AZITHROMYCIN AS MODEL DRUG

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ABSTRACT

Current research has introduced a development of suitable palatability evaluation study by spectroscopic method using mini-column method, for formulation of taste masked Azithromycin tablets by using weak cationic exchange resin viz., Indion-204and/or Kyron T-114, was formulated as fast dissolving tablets[12]. A comparison was revealed with different batches of ion exchange resin, in present investigation with challenging aspects for study of molecular properties like FTIR study, drug release profile, swelling study of Drug resin complex (DRC). Result revealed that there is a strong interaction by complexation of NH^+ group of drug and COO^-, Drug release from DRC in salivary pH was insufficient to impart bitter taste, is established by Uv- Spectroscopic method by mini-column method provided threshold concentration of minimum concentration exerting bitterness, a protocol provides an complete taste masking in both of formulation having Indion-234 and Kyron T- 114 and complete drug release was found at gastric pH 1.2 , Drug release was accelerated in presence of electrolytes. So it can be concluded that all drugs having an amine group can be taste masked by using Kyron T114 and Indion 234.

Keywords: Azithromycin, FDT, Mini-column method, Macrolide antibiotics

INTRODUCTION

The Macrolide[9] inhibit RNA-dependent protein synthesis resulting in bacteriostatic antimicrobial activity. Azithromycin is under macrolide group of antibiotics[11] has greater activity against gram-negativeorganisms, particularly genitourinary pathogens(eg C.trachomatis, U.urealyticum, N.gonorrhoeae, andT.pallidum)[10].

Ion exchange resins are polymeric particles that contain basic or acidic groups, which can form ionic complexes oppositely charged drugs. The resins are insoluble solids that are not absorbed by the body; hence, they do not have significant associated side effects[1]. Ion exchange resins have specific properties like available capacity, acid base strength, particle size, porosity and swelling. On which the release characteristic of the drug from drug resin complex are dependent. The large pore size, the enormous surface area, the number of exchange sites and their hydrophilic nature are the favorable characteristic.

Macro reticular type resins that may be used in the present invention are formed from the copolymerization of methacrylic acid and divinylbenzene. The resulting porous matrix may be carboxylated to give a weakly acidic ion exchange resin. An example of such a resin is Kyron Resin Grade T-114. Macro reticular type of resins by copolymerization of acrylic acid and methacrylic acid, an example of this is Indion 204.

Ion Exchange resin has been used for taste masking of bitter drugs. Borodkin *et al.*[1] prepared high potency Adsorbate of methapyrilene, dextromethorphan, ephedrine, pseudoephedrine by column procedures using a polymethacrylic acid ion exchange resin. Taste evaluation of the adsorbates showed a significant reduction in the bitterness of the drugs. Extreme bitterness of quinolones has been achieved by ion exchange resin such as methacrylic acid polymer cross linked with divinylbenzene[2]. Taste masking of quinolones have been done by using Kyron T104 (methacrylic acid polymer cross linked with divinylbezene) [3, 4].

Efforts have been done for taste masking of macrolide antibiotics with weak cation exchange resin Kyron T114 and/or Indion 204 and involvement of group has also been studied.

MATERIALS AND METHODS[8]

Azithromyci is drug of choice for the present investigation provided as free sample by Alembic ltd., (Baroda, India) and Ion exchange resin are Kyron T-114 got from Corel Pharma[7] Chem., (Ahmedabad, India) Hydrochloric Acid by Qualigen Chemicals, Indion 204 and Indion 234 by Ion exchange India Ltd, Mumbai.

Methodologies

A) Purification of ion exchange resins

All the resins were given a pre- treatment to remove the impurities associated with industrial scale manufacture. The resins were purified by rinsing 10 gm of wet resin with 3 x 5 ml portions of deionized water, 1x 50 ml of 95% ethanol and 1x 50 ml of deionized water. Each stage of treatment lasted 1 hour under magnetic stirring. The resin was then conditioned with 60 ml of 2M NaOH and 60 ml 2M HCl and with deionized water after each treatment. Finally the resins were recovered by vacuum filtration, washed thoroughly with de ionized water and dried. Then ground and passed through sieve number 100 to get a uniform size distribution.

B) Preparation of drug-resinate complex

The method used for masking the taste of Azithromycin is complexation with ion exchange resins like Indion 204(Indion 234), Kyron T-114 as per the following procedure:

Drug and resin were accurately weighed in required ratio. Then slurry of resin was made in demineralised water and stirred for half an hour at 500 rpm, in order to allow the polymer structure to swell uniformly. The drug was made in solution using 10 ml of methanol. Then drug solution was added slowly under stirred condition. The drug resin mixtures were then continuously stirred for 8 to 10 hrs at 500 to 600 rpm and the volume was made up to 100 ml. Several trials were carried out with different ratios of ion exchange resins and different stirring times as shown in Table 1.

Preparation of azithromycin fast dissolving tablets

Azithromycin taste masking is done by using Kyron-T-114 and/or Indion-204 in different ratio of drug. Kyron/Indion was taken in a beaker and stirred for some time with distilled water, then added with Azithromycin dihydrate and stirred for the next two hours, forming a taste masking slurry.

The slurry is dried and made into granules by passing it through sieve number 30.Mouth dissolving tablets of Azithromycin dihydrate were prepared by the conventional direct compression technique using Kyron-T-114, crospovidone, croscarmellose sodium, and sodium starch glycollate as superdisintegrants. The composition of each formulation is given in Table. 1

Evaluation of drug – resin complex

1) Drug entrapment efficiency determination

Drug resin complex equivalent to 100 mg of pure drug was dissolved in 0.1 N HCl in 100 ml volumetric flask. The mixture was sonicated for 30 min, filtered and drug content was estimated using assay procedures given in estimation of Azithromycin**.** Results for drug Entrapment efficiency are depicted in Table 2.

2) Drug release from drug resin complex

Drug release from DRC (1:3) in 0.1 N HCl was determined using a USP XIV type II dissolution apparatus. Accurately weighed DRC equivalent to 100 mg of macrolide antibiotics was added to 900 ml 0.1 N HCl for 60 minutes (100 rpm, 37°C). A 10-ml sample was withdrawn, filtered and analyzed using assay procedures given in 2.5.2. Drug release from the DRC was also performed in 10 ml of pH 6.8 buffer solution (simulated saliva fluid) by adding 100 mg of the DRC to a test tube, shaken for 60 seconds, filtered and filtrate was assayed for drug[35]. Results for drug release from DRC are given in Table 2.0.

3) Molecular complex of drug resin complex

Infrared spectra of DRC, drug, Indion 204 sand Kyron T-114, were obtained using Fourier-transform infrared (FTIR) spectroscopy [FTIR-8400S, CE, Shimadzu]. The pellets were prepared on KBr press, and the spectra were recorded over the wave number 4000 to 400 cm^{-1}. The spectra were comparatively analyzed to check the appearance /disappearance of certain peaks that may be indicating of complex formation between drug and resin, as well as the extent of Complexation. Results of FT IR studies are given in Fig 1, 2, and 3. Characterization of complexation is provided in Table 3, 4 and 5.

4) Micromeritics property of drug resin complex

Physical characteristics acts as the behavior of drug release and stability as dosage form. Bulk density which is determined by weight of granules/ untapped volume, tapped density which is determined by weight of granule to its tapped volume. Angle of repose is to determine its flow ability, by fixed funnel method; physical properties are tabulated in Table 6.

Post compressible studies[13]:

1) Friability test

A high amount of attrition during the coating procedure could modify the release behaviour due to the incorporation of small particles in the film. A friability of less than 0.8 % is generally accepted for tablets, but for granules this value could be higher due to the higher surface area/unit and subsequent involvement of frictional force[5].

Friability of Granules was determined using Roche friabilator. Two gm granules having size between 40# to 60# were placed in the friabilator. It was subjected for 100 revolutions at the speed of 25 rpm. Granules were than subjected to size analysis and particles passing through 60# sieve were collected and weighed. Results of Friability are shown in Table 7.

2) Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling.

The hardness of the tablets was determined using Pfizer hardness tester. It is expressed in KP. Three tablets were randomly picked and hardness of the tablets was determined and tabulated in table 7.

3) *in-vitro* dispersion time (with simulated salivary fluid)

This test is performed to ensure disintegration of tablets in the salivary fluid, if it is to be used as a fast dissolving tablet. In vitro dispersion time was measured by dropping a tablet in a measuring cylinder containing 6ml of simulated salivary fluid of pH 6.8(Table 9).

4) Water absorption ratio or wetting time

A piece of tissue paper folded twice was placed in a small petridish containing 6 ml of water. A tablet of known weight was put on the paper and the time required for complete wetting of tablet was measured. The wetted tablet was then weighed, water absorption ratio R was determined using the following equation. Results are tabulated in Table 9.

Where, W_b- W_a/ W_a

Wb = weight of tablet before water absorption

Wa is= weight of tablet after water absorption

5) Weight variation

10 tablets were weighed individually, average weight of tablets was calculated and their upper and lower limits were calculated and results are tabulated in Table 8.

$$\text{Weight variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

6) Drug release study by dissolution study

Drug release data was obtained in simulated salivary pH 6.8 and simulated gastric pH 1.2 in USP II dissolution apparatus with 500 RPM, An evident is to provide the desired release rate at which resin swells and dissociate leaving drug.

Estimation of Azithromycin

Azithromycin (250 mg) was accurately weighed and transferred to a 100 ml volumetric flask. It was dissolved in glacial acetic acid (20 ml, 3 M), and diluted to 100 ml with distilled water. An aliquot (5.0 ml) was further diluted with water in 50 ml volumetric flask, to obtain the final concentration of 250 µg/ml. In a 10 ml volumetric flask, standard Azithromycin solution (2.0 ml) and glacial acetic acid solution (1.0 ml) were pipette successively. Potassium permanganate solution (0.25 % w/v, 0.025 ml) was added. The reaction flask was heated on a water bath at 37°C for 10 min. Excess of potassium permanganate was neutralized with oxalic acid (10 % w/v). Ammonium acetate- acetyl acetone reagent (2.0 ml) was added to it, and mixed thoroughly. The reaction flask was heated on a water bath at 37°C for 1 min, cooled, and the volume was adjusted up to the mark with distilled water. Absorbance of the colored solution was scanned on UV visible spectrophotometer from 600 nm to 200 nm, against reagent blank. Maximum absorbance was obtained at 412 nm.

Ammonium acetate- acetyl acetone reagent was prepared by dissolving ammonium acetate (30 g) in water (50 ml). Acetyl acetone solution (1.0 ml) was added, and the final volume was adjusted to 100 ml with water.

7) Taste evaluation of drug resin complex using UV spectroscopic method by mini-column method

Difficulty in analyzing bitterness of tablets due to its varied shape and size, problems can be avoided by crushing tablets and tapping in the powder form. High tapping frequency limits penetration of phosphate buffer in the compacted mass. Differently varied the high tapping frequency set at 3, 10 and thirty times with, low penetration of phosphate buffer flow rate at 1, 1.3, 1.5ml.

Mini-column consists of two separate columns, upper and lower chamber. The inner side of nozzle (lower column) was closed with an accurately weighed piece of wet absorbent cotton. The weight of absorbent cotton piece was kept constant for all samples. RDTs were crushed in mortar & pestle then the powdered sample was filled and packed in the column by tapping. After tapping the column 30, 10 or three times, accurately weighed absorbent cotton was packed on the sample bed to eliminate sample motion. The weight of absorbent cotton piece was kept constant for all samples. Upper column was filled with phosphate buffer and attached to lower column. The phosphate buffer flowed through lower column at 1.5 ml/min. The residence time of the phosphate buffer was 3 min. The elute was

collected at 2 min intervals for 5 min. Each elute was used as sample solution and further evaluated using UV spectrophotometer (Shimadzu UV visible spectrophotometer) at 412 nm. The bitterness score of mini-column was compared with human volunteer test.

The tapping frequencies of column and flow rate of test solution were assumed to influence the mini-column method results. Higher the tapping frequency lower be the release of Erythromycin, Likewise higher be the flow rate, lower be the release rate and hence optimization is made to get adjust with higher limit of tapping frequency and lower penetration rate.

Data interpretation

1) mini- column method even though a spectroscopic mean of evaluating bitterness, to calculate Threshold concentration which exhibits bitterness was provided a human volunteer showed, In table 10.

2) Tapping frequency was set at 3, 10, 30 times and flow rate at 1, 1.3, 1.5ml/min.

3) Optimization was done with flow rate and carried with three different tapping frequency and results were tabulated in table 11.

Estimation of threshold concentration of Azithromycin

Drug release from Drug resin complex (DRC) was performed in 10ml of pH 6.8 buffer solutions by adding 100mg of DRC in test tube, shaken for 60 sec, filtered and assayed for spectroscopic evaluation.

RESULTS AND DISCUSSION

Complexation between the drug and resin is essentially a process of diffusion of ions between the resin and surrounding drug solution. As the reaction is an equilibrium phenomenon, maximum efficacy is achieved in batch process. Macrolide antibiotics release from drug-resin complex was observed in average salivary pH of 6.8, and at gastric pH of 1.2, separately. In vitro drug release in average salivary pH of 6.8 was 4.39%(< 5%) with Kyron T-114 and 3.9% in case of Indion 204 within 60 seconds.[6] the presence of exchangeable ions of ionizable electrolytes in the salivary fluid may be responsible for this release. At gastric pH (1.2), 90% of macrolide antibiotics were released within 60 minutes. The hypothesis that the drug-release equilibrium, similar to drug loading, is highly dependent on the physiological pH can be applied for taste masking without affecting the dosage form characteristics[5]. A result reveals that drug entrapment of resin was found to be 91±2.72% and 88±1.54% in case of drug Kyron complex and Indion 204 complex, Drug release of DRC was established in pH 1.2(simulated gastric fluid) and found around 90% of entrapped drug is been released. Micromeritics property of Drug resin complex reveals that the lower values of bulk density observed for both granules are favorable for obtaining higher porosity when compressed into tablets, which in turn is favorable for faster disintegration. Molecular property of drug resin complex reveals that there is interaction between the NH^+ group of Azithromycin and functional group COO^- forming complexation and releasing drug at 1.2 pH. Taste evaluation using spectroscopic method results reveals that less than 5%(4.67%) of drug release in salivary fluid, which is due to the exchange of electrolyte in ion exchange resins and found no bitter taste for 60 secs. Taste evaluation in phosphate buffer reveals that the release rate is less to exhibit the bitterness.

CONCLUSION

In the present study, an attempt was given to mask bitter taste of Macrolide antibiotics by Kyron T-114 and/ or Indion234 (Cation exchange resin). Drug release from DRC in salivary pH was insufficient to impart bitter taste. Complete drug release was observed at gastric pH. This approach can be utilized for taste masking of bitter pharmaceutical ingredients leading to improved patient compliance. Complete drug release was observed at gastric pH in 2 hours. The drug release was accelerated in the presence of electrolytes.

Infrared spectroscopy revealed complexation of –NH (drug) with Indion 234 and with Kyron T-114. FTIR study revealed that there is interaction between carboxylic group of ion exchange resin and amine group of Macrolide antibiotics. Drug entrapment was above 70% for all Macrolide antibiotics studied. So it can be concluded that all drugs having an amine group can be taste mask by using Kyron T114 and/or Indion 234 and Indion 234.

Table 1: Composition of fast dissolving tablets

S. No	Ingredients	FDT1	FDT2
1	Azithromycin dehydrate + Indion 204	104+ 312	…
2	Azithromycin dehydrate + Kyron 114	…	104+ 312
3	MCC pH 102 grade	50	50
4	Mannitol	80	80
5	Indion 204	7	…
6	Kyron 114	….	7
7	Potassium carbonate	44	44
8	Cross povidone	…	….
9	Magnesium stereate	2.5	2.5
10	Talcum	5	5
11	Aerosil	3	3
12	Aspartame	10	10
13	Flavour	12.5	12.5

Table 2: Drug entrapment and percentage drug release

Properties of drug resin complex		
Drug	**Drug entrapment**	**% Drug release in 1 hr**
Azithromycin- Kyron T-114 resin complex	91±2.72%	79±1.48%
Azithromycin- Indion 204 resin complex	88±1.54%	84±0.98%

A. Characteristics band assignment of Azithromycin (pure drug) Infrared spectrum:

Table 3: FTIR of pure drug

Frequency	Assignment
2453 cm^{-1}	γ OH stretching (broad- intermolecular hydrogen bonding)
2968-2935cm^{-1}	γ CH(aliphatic) stretching vibration
1725cm^{-1}	γ C=O carbonyl ether stretch

1458cm^{-1}	CH_3 – O (alkyl ether)
1376cm^{-1}	CH_20 (alkyl ether)
1165cm^{-1} & 1050 cm^{-1}	COC functionalities represents as asymmetrical & symmetrical aliphatic ether respectively

B. Characteristics band assignment of AZI- Kyron 114 resonates complex:

Table 4: FTIR of drug- Kyron T- 114 complex

Frequency	Assignment
1764cm^{-1}	Corresponds to C=O stretching of aryl acid
1602 cm^{-1}	Due to aromatic stretching C−C
2308 & 2347 cm^{-1}	Number of overtones
3500- 3600 cm^{-1}	OH stretching peak is absent in drug resin complex, because there is no free OH groups

C. Characteristics band assignment of AZI – Indion 204 resonates complex:

Table 5: FTIR of drug- Indion 204 complex

Frequency	Assignment
1746.23cm^{-1}	Due to – COO stretching of resins
3449.06 cm^{-1}	Due to – NH stretching
2879 cm^{-1}	γ CH(aliphatic) stretching vibration
1648 cm^{-1}	Due to –C=0 streching

Table 6: Micromeritics property of drug resin complex granules

Formulation	Bulk density (gm/ml)	Angle of repose (θ)	Compressibility (%)	Hauser's ratio
FDT1	0.434	31.78	20.54	0.78
FDT2	0.435	35.27	23.60	0.84

Table 7: Friability and hardness testing

Formulation	Hardness Test (kg/ cm^2)	Friability Test (%) n= 10	Thickness Test (mm) n= 4
FDT1	4.28± 0.28	0.33 ± 0.02	3.60±.05
FDT2	3.56 ± 0.4	0.32 ± 0.04	3.4 ± 0.005

Table 8: Weight variation

Sl.no	FDT1	% weight variation	FDT2	% weight variation
1	597	3.02	600	0.566
2	573	-1.03	603	1.06
3	602	3.79	604	1.22
4	595	2.76	585	-1.98
5	598	3.28	591	-0.94

Table 9: *in-vitro* dispersion time

Formulation parameters	Resonates with Indion 204	Resonates with Kyron T-114
in- vitro disintegration time (water)	16 ± 1.5	20 ± 1.0
in- vitro disintegration time (simulates salivary fluid)	14 ± 1.0	19 ± 2.0
in- vitro dispersion time	11 ± 1.5	17 ± 1.5
Wetting time	4 ± 1.0	7 ± 1.5

Table 10: Threshold concentration and threshold Abs. of standard Erythromycin solution

Conc.	I	II	III	Mean
0.347 mg/ml	0.413	0.425	0.420	0.419 ± 0.008

Table 11: Bitterness evaluation using UV spectroscopic method

Formulation	FDT1 Time (Mins)			FDT2			FDT3		
	5	**10**	**15**	**5**	**10**	**15**	**5**	**10**	**15**
Tapping 3	0.134	0.235	0.289	0.124	0.204	0.257	0.453	0.489	0.523

10	0.121	0.241	0.295	0.111	0.212	0.231	0.439	0.468	0.503
30	0.116	0.219	0.240	0.109	0.2	0.224	0.414	0.436	0.5

Fig. 1:

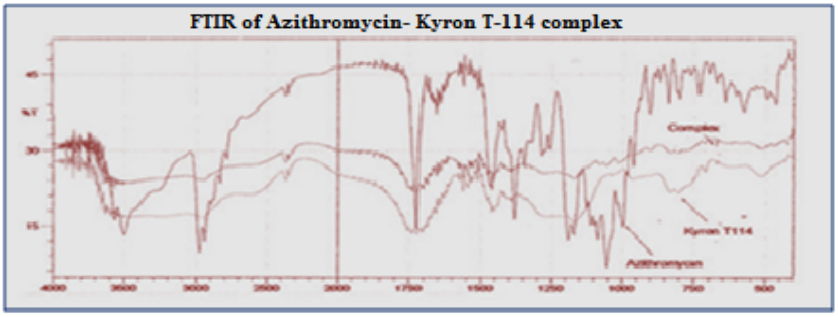

Fig. 2:

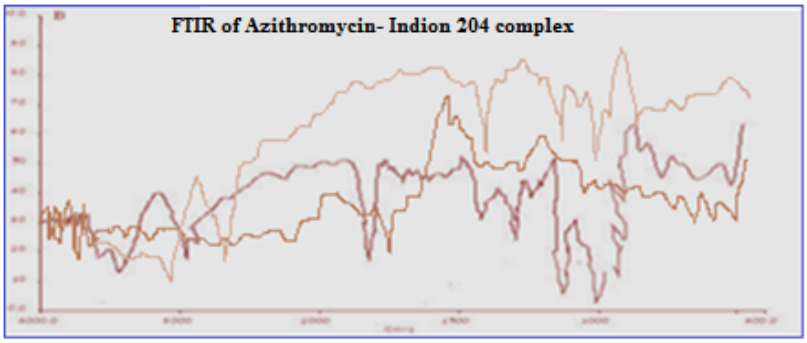

Fig. 3:

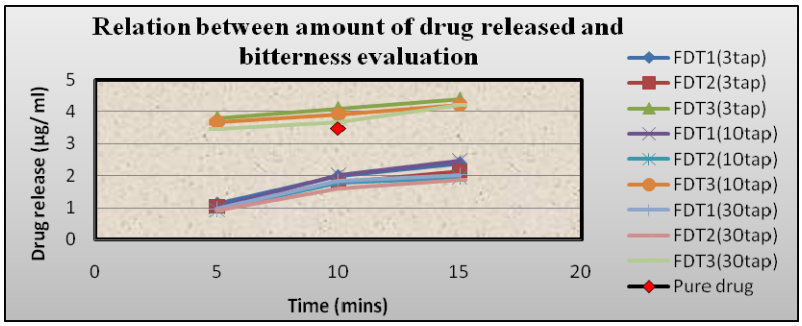

Fig. 4: Relationship between Amount of Release and Results of Sensory Test of FDTs Using Mini-column Method

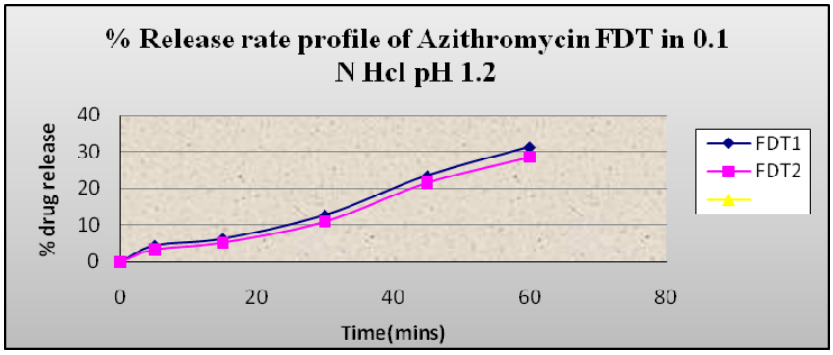

Fig. 5: Drug release study at pH 1.2(simulated gastric pH)

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