COMPARATIVE *IN VITRO* EVALUATION OF MARKETED AND FABRICATED TABLET FORMULATIONS OF CIPROFLOXACIN – TINIDAZOLE COMBINATION

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Summary

Ciprofloxacin hydrochloride has a wide spectrum of antibacterial activity. Tinidazole has antiprotozoal and antibacterial actions. Both drugs having almost matching pharmacokinetic properties are suitable rational combination as tablet dosage form. In the present study one tablet dosage form is fabricated (CF) and comapared with three marketed tablet dosage (CF1, CF2 and CF3) forms in evaluations. The fabricated tablet dosage (CF) showed results in dissolution study superior to all the three (CF1, CF2, and CF3) marketed products and subjected to stability study by storing at 40°C(dry box)/40°C/90% RH (environmental chamber), room temperature and in refrigerator for 45 days. There was no significant alteration in description, disintegration time and dissolution test during stability study and thus, CF was found suitable, stable and superior to CF1, CF2, and CF3.

Introduction

Ciprofloxacin is bactericidal and acts by inhibiting a subunit of DNA gyrase (topoisomerase) which is essential in the reproduction of bacterial DNA.[1,2]. Tinidazole is a nitroimidazole derivative and has antibacterial actions[3,4]. 40 drug substances with proven or suspected bioavailability problems were reported. In many of examples cited, the product confirmed to label claims but drug simply was not available to the body[5,6]. Levy studied on the comparative dissolution of different brands of tolbutamide and concluded that dosage form was responsible for the difference in therapeutic response[7]. Varley reported slower rate of dissolution to produce lower blood levels and to provide less hypoglycemic effect of tolbutomide[8]. Laboratories studies indicated that the dissolution rate of drug from larger tablets was slower than from the smaller tablets[9]. Brice et.al. showed non-equivalency of various brands of oxytetracycline produced by suppliers, certified by FDA[10]. Generic equivalence and inequivalence of oral products are discussed by Wagner.[11,12] By observing the demand of this combination, especially for diarrhoea, the present study is undertaken to formulate a tablet dosage form better than existing in Indian market.

Materials

Ciprofloxacin hydrochloride (Amber chemicals), tinidazole (Gufic chem.. pvt. Ltd), starch (Maize Products), lactose, (Lactose India Ltd.), microcrystalline cellulose (Merk), talc (Mittlal Polymer), and magnesium stearate (Mittlal Polymer) were procured from commercial sources and used as received.

Methods

Table 1
Formulation of Ciprofloxacin - Tinidazole Combination Tablet Dosage Form CF

S.No	Ingredients	mg per tablet
	[A]	
1.	Ciprofloxacin Hydrochloride (Equivalent to Ciprofloxacin)	290 (250)
2.	Starch	144
3.	Lactose	25
4.	Microcrystalline Cellulose	10
5.	Talc	1.1
6.	Magnesium Stearate	15
	[B]	
7.	Tinidazole	300
8.	Starch	10
9.	Microcrystalline Cellulose	7.5
10.	Lactose	7.5

A. Ciprofloxacin Hydrochloride Granules

Ciprofloxacin hydrochloride, microcrystalline cellulose, talc, lactose and starch were mixed together (Table 1). Starch was used for three purposes, diluent, binding agent (Paste) and lubricant. Starch paste was prepared and mixed to the above ingredients. The dough mass was allowed to pass through sieve # 14 to make granules and granules were dried. The dried granules were passed through sieve # 22 to get fine granules.

B. Tinidazole Granules

Tinidazole, microcrystalline cellulose and lactose were mixed together (Table 1). Starch paste was prepared. Starch paste was mixed with the above ingredients and passed through sieve number 14 to get granules. Granules were dried and passed through sieve number 22 to get fine granules. Talc and magnesium stearate were added to avoid sticking and picking problems during compression.

Compression

Both ciprofloxacin hydrochloride granules [A] and Tinidazole granules [B] were mixed together. Magnesium stearate and starch were used as glidants and lubricants. Granules were compressed by using 18/32 punches in a Cadmach machine.

Table 2
Coating Materials for the Formulation of Fabricated Tablets CF

S. No	Ingredients	mg per Tablet
1.	Pharmacoat	20 mg
2.	Titanium Dioxide	5.6 mg
3.	Talc	4.4 mg
4.	PEG 6000	2.2 mg
5.	Colour – Sunset Yellow	6.0 mg
6.	Isopropyl alcohol	1.2 ml
7.	Methylence Chloride	0.26 ml

Film Coating

Ingredients used for film coating of tablets are given in Table 2. They were dissolved in isopropyl alcohol and then methylene chloride was added. Film coating was done in a conventional coating pan using pilot type – 59 gun for spraying. The rotation of pan was at 4rpm.

Evaluation

Dissolution study

Ciprofloxacin hydrochloride

900 ml water was taken as dissolution medium, rotating paddle at 50 rpm for 30 minutes in a dissolution apparatus. The absorbance of diluted medium taken after 30 minutes was measured at λ_{max} of 278 nm for knowing the amount and percentage of drug dissolved.

The specified limit is not less than 80% drug dissolved in 30 minutes.

Weight Variation

It was conducted as prescribed in Indian Pharmacopoeia 1995 for tablets.

Friability Test

20 tablets were weighed accurately and rotated in Roche Friabilator for 4 minutes. Tablets were removed and weighed. The weight loss is calculated.

Disintegration Test

Disintegration test was conducted using USP XXII apparatus. The present tablet formulation is film coated, so it was conducted for 30 minutes.

Assay

Ciprofloxacin Hydrochloride

Powdered tablets were dissolved in water. Appropriate dilution was made by water and absorbance was observed at λ_{max} of 276 nm.

Tinidazole

For tinidazole assay, method prescribed in Indian Pharmacopoeia 1995 was followed.

Studies on Granules

Bulk and tapped density, compressibility index, angle of repose, compression test, moisture content and content assay of granules were studied before compression and found suitable for compression.

Stability Study

The CF tablet formulation was stored at 40°C (dry box), 40°C/90% RH (environmental chamber), room temperature and refrigerator for 45 days. Description, disintegration time, dissolution and assay were carried out during stability study.

Results and Discussion

The present investigation was undertaken to formulate tablet dosage form of ciprofloxacin and tinidazole combination and compare it with three brands of tablet formulations in Indian market. General description of marketed formulation (Table 3), and weight variation of marketed tablets (Table 4) are presented. Average assay of CF1, CF2 and CF3 for ciprofloxacin are 96.90%, 94.24% and 88.52% and for tinidazole are 94.68%, 93.57% and 93.02% respectively. Average dissolution release of ciprofloxacin after 30 minutes for CF1, CF2, and CF3 are found 94.16% 94.01% and 92.61% respectively. Disintegration test of marketed product showed results of 6 minutes, 32 seconds for CF1, 6 minutes and 12 seconds for CF2 and 7 minutes and 28 seconds for CF3.

Table 3
General Description of the Marketed Tablet Formulations of Ciprofloxacin – Tinidazole Combination

S. No	Description	CF1	CF2	CF3
1.	Colour	Yellow	Pale Yellow	Pale Yellow
2.	Odour	Characteristics	Characteristics	Characteristics
3.	Taste	Bitter	Bitter	Bitter
4.	Shape	Oval Shaped	Round shape	Oval shaped with scored in the middle on one side

Table 4

Weight Variation Test of the Marketed Tablet Formulation of Ciprofloxacin- Tinidazole Combination

S.No	Commercial formulations	Average weight of tablet (g)	% weight variation	
			Minimum	Maximum
1.	CF1	0.7241	0.6878	0.7603
2.	CF2	0.6172	0.5863	0 .6480
3.	CF3	0.6838	0.6496	0.7179

Table 5
Physical Parameters Including Assay of Fabricated Core Tablets of Ciprofloxacin – Tinidazole Combination
CF

S.No	Description	Weight Variation	Disintegration	Friability in %	Thickness in mm	Hardness in kg/cm^2	Dissolution in %	Assay in %	
							Ciprofloxacin	C	T
1	CF	Pale Yellow coloured, oval shaped tablet, and scored in the middleon one side	3 min, 6 sec	0.32	5.38	6.34	96.19	95.81	99.43

C= Ciprofloxacin, T = Tinidazole

Table 6

Physical Parameters Including Assay of Fabricated Film Coated Tablet of Ciprofloxacin – Tinidazole Combination CF

S. No	Weight Variation	Disintegration Time	Dissolution release in %	Assay in %	
			Ciprofloxacin	C	T
1.	Passes	7 min, 30 sec	96.53	97.16	99.48

C= Ciprofloxacin, T = Tinidazole

Studies done on granules of CF formulation were found suitable and useful for compressing granules in tablet dosage form. Physical parameters and important results of core tablet of CF is presented in Table 5 and of coated CF formulation is presented in Table 6. CF, CF1, CF2 and CF3 passes and complies all requirement of evaluations except CF3 which showed very low level of variation in assay for ciprofloxacin (88.52%) but it has shown in 30 minutes 92.61% drug dissolved. Hardness of fabricated CF was obtained by Monsanto hardness tester.

Table 7

Evaluation of Stability of Fabricated Tablet Formulation CF After 45 days

S. No	Description	40°C		Room Temperature		Refrigerator		40°C / 90 % RH	
1.	Appearance	No change		No change		No change		No change	
2.	Disintegration Test	9 min, 3 sec		7 min, 26 sec		6min, 26 sec		5min, 4 sec	
3.	Dissolution Release in %	C	T	C	T	C	T	C	T
		95.07		95.10		95.33		94.69	
4.	Assay in %	97.01	96.23	96.84	96.18	96.68	95.94	95.58	96.17

C= Ciprofloxacin, T = Tinidazole

Comparison of results of dissolution studies and assay of CF1, CF2, CF3 and CF (Table 6) shows that fabricated tablet dosage form CF is superior to all three marketed products. From Table 7, it is found that CF is well stable in all respects. Thus the present study is highly illustrative and useful for formulation of ciprofloxacin tinidazole combination tablet dosage form better than three popular brands of Indian market.

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