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RESEARCH ARTICLE

Formulation development and dissolution enhancement of Compeba-400 (Metronidazole-400) tablet.

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Abstract

The reason of this study is to diminish or entirely end of binding and capping dilemma of metronidazole tablet. Metronidazole is an antiemetic and prokinetic drug used in the management of motion sickness in adults and children. As meticulousness of dosing and patient's compliance become imperative prerequisite for quick relief from motion sickness. Fast dispersible tablets disintegrate either rapidly in water, to form a stabilized suspension, or disperse instantaneously in the mouth to be swallowed without the aid of waters. A direct compression technique was used to prepare these types of tablets using diverse super disintegrants. An endeavor was made in the current work to formulation development and enhancement dissolution of metronidazole (COMPEBA-400) tablets. This research work is also investigated a new dosage form of metronidazole with lofty dissolution rate and squat cost. To afford the patients with the most conventional mode of administration, there was a stipulation to build up tablet dosage form, chiefly one that disintegrants and dissolves/disperses in body fluid administered with water. Both the derivatives Methyl Chloride and Isopropyl alcohol have tremendous film forming and coating properties. By using MCC at the place of lactose & sugar we can dwindle the tablet price and augment dissolution rate. The compressed tablet is the most accepted dosage form in use these days. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. By using CCS in lubrication we can amplify the dissolution rate of tablet because CCS helps to suspend the tablet rapidly from edge and centre of the tablet. Hefty amount of binder like as starch, gelatin, glucose and polyvinylpyrrolidone (PVP) in paste thwart to the tablet from capping. No significant changes were pragmatic when drug content were analyzed after one month stability testing.

Keywords: Metronidazole, Crospovidone, Croscarmellos sodium, Microcrystalline cellulose, DCP, Isopropyl alcohol.

Introduction:

Recent advances in novel drug delivery system aims to enhance the safety and efficacy of the drug molecule by formulating a dosage form being convenient for administration. Difficulty in swallowing experienced by patients such as pediatrics, geriatrics, bedridden, disabled and psychiatrics, including motion sickness and sudden episodes of allergic attacks, hence resulting in higher incidence of noncompliance and ineffective therapy. To improve the quality of life and treatment compliance of such patients, orally disintegrating or fast disintegrating tablets (FDT) dosage form is a better alternative for oral medication. FDTs are solid dosage form containing medicinal substances, which disintegrants rapidly, usually within matter of seconds when placed in upon tongue requiring no additional water to facilitate swallowing. Chemically, Metronidazole is, 1-(β-hydroxyethyl)-2-methyl-5-nitroimidazole, an oral synthetic antiprotozoal and antibacterial agent which inhibits nucleic acid synthesis. It had especially high activity *in vitro* and *in vivo* against the anaerobic protozoa against T. vaginalis and *E. histolytica* . Metronidazole is also used as a gel preparation in the treatment of the dermatological conditions.[1,2,3]The poor water solubility of the drug gives rise to difficulties in the formulation of dosage form leading to variable dissolution rate .Hence it was selected as a model drug. In the present work an attempt has been made to prepare MDTs of metronidazole using superdisintegrants like Croscarmellose, Crospovidone pre gelatinized starch in different concentrations.

Materials and Methods:

Materials:

Metronidazole was obtained from Indian Drugs & Pharmaceutical Ltd., Gurgaon. Crosscarmellose sodium, Starch, MCC, DCP and SLS were also obtained from Indian Drugs & Pharmaceutical Ltd., Gurgaon. All other reagents and chemicals usedwere of analytical grade.

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Methods:

Preformulation study[4]:

Preformulation studies are the first step in the rational development of dosage form of a drug substance. The objective of preformulation studies are to develop a portfolio of information about the drug substance, so that this information useful to develop formulation. Preformulation can be defined as investigation of physical and chemical properties of drug substance alone and when combined with excipients. Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture, and pharmacokinetic-biopharmaceutical properties of the resulting product.[36]

Formulation of Metronidazole Tablet:

Dry mixing:

Weighed the Metronidazole powder, CCS (croscarmelose sodium), starch, DCP (dibasic calcium phosphate), MCC (microcristaline cellulose), SLS (sodium lauryl sulfate) and passed it through 60 # screen and mixed it properly.

Paste Solution:

Weighed the starch, gelatin, methyl parabene and propyl parabene and then make the paste separately of starch and gelatin and than added methyl parabene and propyl parabene in the starch paste and mixed continuously on the heater.

Mixing:

Add the paste solution in the dry mixing container which has metronidazole powder, CCS, DCP, MCC, and SLS mixed it properly.

Granulation:

Finally the material was passed through 10 # screen and granules were collected then spread the granules in the tray and put it in the electrical air dryer at temperature 40 degree C for 30 minutes.

Lubrication:

Before lubrication the granules were passed through 14 # screen and the very fine granules were collected and then weighed talc, aerosil, CCS and magnesium stearate accurately and passed it through 60 # screen. All the materials and granules were transferred into double cone blander for mixing uniformly.

Compression:

The resulting granules were transfer into single punch tablet machine and compressed with 12 mm punch size into convex shape tablets. Formulations of tablets were represented in Table no.14

Batches of Metronidazole using various super-disintegrants:

Various superdisintegrants and binders were used for formulation of metronidazole tablets. In these formulation crospovidone, croscarmellose sodium was used as a superdisintegrant. And starch, mcc (microcristaline cellulose), sugar etc were used as a binder.[5]

Evaluation of metronidazole tablets:

General Appearance:

The general appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Include in are tablet's size, shape, colour, presence or absence of an odour, taste, surface texture, physical flaws and consistency and legibility of any identifying marking.

Size and Shape:

The size and shape of the tablet can be dimensionally described, monitored and controlled.

Tablet thickness:

Tablet thickness is an important characteristic in reproducing appearance and also in counting by using filling equipment. Some filling equipment utilizes the uniform thickness of the tablets as a counting mechanism. Ten tablets were taken and their thickness was recorded using micrometer or verniar caliper.[6]

Uniformity of weight:

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

Sr. No.	Average weight of Tabs. (mg)	Maximum percentage difference allowed
1	130 or less	10
2	130-324	7.5
3	More than 324	5

Hardness:

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of tablets. In the present study the hardness of the tablet was measured using Monsanto hardness testers.

Friability testing:

The crushing test may not be the best measure of potential behavior during handling and packaging. The resistance to surface abrasion may be a more relevant parameter. Friability of each batch was measured in "Roche friabilator". Ten preweighed tablets were rotated at 25 rpm for 4 min, the tablets were then reweighed and the percentage of weight loss was calculated using following formula.[7]

%Friability = loss in weight / Initial weight x 100

In-vitro disintegration time:

The in-vitro disintegration time was determined using disintegration test apparatus. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time in seconds taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds.[7]

Weight variation test of tablets:

Twenty tablets were taken and weighed individually by an analytical balance. The average weight of the tablets was calculated. Then % of weight variation is calculated by using the following formula.

$$\% \text{ of wt variation} = \frac{\text{Individual weight} - \text{Average weight}}{\text{Average weight}} \times 100$$

Potency determination of tablets:

(a) Preparation of standard solution: 100 mg of standard metronidazole was weighed accurately in an analytical balance and was taken in a 100 ml volumetric flask. 50 – 60 ml of 1 N HCl was added and was shaken mechanically for 30 min. The volume was made upto the mark with the same solvent . 1 ml of the above solution was diluted to 100 ml with 0.1 N HCl solution.

(b) Preparation of assay solution: 20 tablets were weighed and powdered in a mortar with a pestle. An amount of powder equivalent to 100 mg of metronidazole was transferred in a 100 ml volumetric flask. 50 – 60 ml of 1 N HCl was added and was shaken for 45 min. The volume was made upto the mark with the same solvent and filtered with whatmann filter paper. 1 ml of the filt- ered solution was diluted to 100 ml with 0.1 N HCl solution.

Calculation:

The absorbance of both standard and sample were measured in a suitable UV- VIS spectrophotometer at 253 nm using 0.1 N HCl solution as blank. Each sample was run in duplicate and average of the results was taken in to consideration.[8]

$$\text{Potency of sample} = \frac{\text{Absorbance of sample} \times \text{Weight of standard}}{\text{Absorbance of standard} \times \text{Weight of sample}} \times \text{Purity of standard}$$

Dissolution test:

Standard USP or IP dissolution apparatus have been used to study in vitro release profile using rotating paddle. In vitro release rate study of film coated tablet of Metronidazole was carried out using the Apparatus 2 (Paddle apparatus) method. The dissolution apparatus was covered with the black color polythine to protect the solution from light. The dissolution test was carried out using 900 ml of 0.1 M HCl, at 37 $\pm$ 0.5^0C and 100 rpm for 60 min. A sample (5 ml) of the solution was withdrawn from the dissolution apparatus at 2, 4, 6, 8 and 10 min and withdrawn volume was replaced with fresh dissolution media. The withdrawn samples diluted with dissolution medium and then filter it with whatman filter paper and assayed at 253 nm. The % release of Metronidazole was calculated. The observation for different batches and the percentage release of Metronidazole with respect to time for each batch were calculated.

In-Vitro drug release:

Release of the drug *in vitro*, was determined by estimating the dissolution profile.[9]

Stability studies of Metronidazole tablets:

Accelerated Stability Testing:

The stability studies of formulated tablets were carried out at 40°C and at room temperature for one month. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The stability studies were carried out when the room temperature was 20 to 25°C. The different parameters that were studied are in vitro disintegration time, wetting time, drug content and in vitro dissolution rate.[10]

Results:

Organoleptic Characteristics:

The color, odor, and taste of the drug were characterized and recorded using descriptive terminology; the results were shown in the Table No 12.

Properties	Results
Description	Crystalline powder
Taste	Taste less
Odor	Odor less
Colour	Yellowish

Table 1: Results of Organoleptic properties:

Ingredient	M. Ph. Batch- 1	M. Ph. Batch- 2	M. Ph. Batch- 3	M. Ph. Batch- 4
Metronidazole	400	400	400	400
Starch(in dry mixing)	20	13	30	25
Starch (in paste)	14.44	30	--	21
Croscarmellose sodium in dry mixing)	10	--	--	--
Croscarmellose sodium (lubrication)	10	20	20	5
MCC	10	10	12.5	12.5
DCP	15	7	10	8
SLS	5	--	--	1
Talc	5	5	5	6
Mg stearate	3	3	3	3
Aerosil	2	2	2	3
Gelatin	5	10	--	8
Methyl Paraben	0.6	0.6	0.6	0.6
Propyl paraben	0.06	0.06	0.06	0.06
Water (for paste in ml.)	40	80	--	75
PVP- K30	--	--	17.5	--
IPA (Isopropyl Alcohol)	--	--	60	--
Lactose	--	--	--	17
Sugar	--	--	--	3

Table 1: Ingredients and batches, All the quantities are in mg.

Batch code	Bulk density	Tapped density	Angle of repose	% compressibility	Hausner's ratio
M.Ph.Batch-1	**0.58**	**0.68**	**25.61**	**14.71**	**1.172**
M.Ph.Batch-2	**0.56**	**0.67**	**25.07**	**16.42**	**1.196**
M.Ph.Batch-3	**0.55**	**0.64**	**24.68**	**14.06**	**1.164**
M.Ph.Batch-4	**0.53**	**0.62**	**24.50**	**14.52**	**1.170**

Table 2: Evaluation of the powder blend for all batches:

Parameters	Batch 1	Batch 2	Batch 3	Batch 4
Hardness (kg/cm^2)	**1.0**	**3.0**	**2.8**	**3.2**
Friability (%)	**Not done**	**0.22**	**0.31**	**0.19**
Thickness(mm)	**5.0**	**5.1**	**4.9**	**4.7**
Disintegration time (s)	**60**	**68**	**73**	**70**
Weight Variation	**Not done**	**Pass**	**Pass**	**Pass**
Dissolution Rate(%)	**Not done**	**101.23 (max.) 92.99 (min.)**	**99.98 (max.) 90.98 (min.)**	**100.32 (max.) 91.95 (min.)**

Table 3: Evaluation parameter of metronidazole tablets:

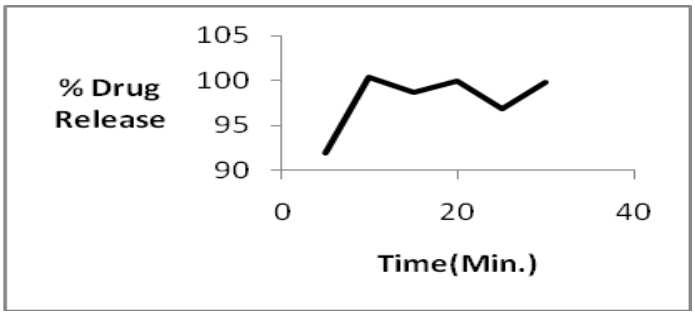
Parameters	Controlled	After 15 days	After one months	Controlled
Drug Content (%)	101.23	100.62	99.34	101.23
In-Vitro Disin. Time (Sec)	68	74	134	68

Table 4: Stability parameters of formulation batch-2 stored at room temperature:

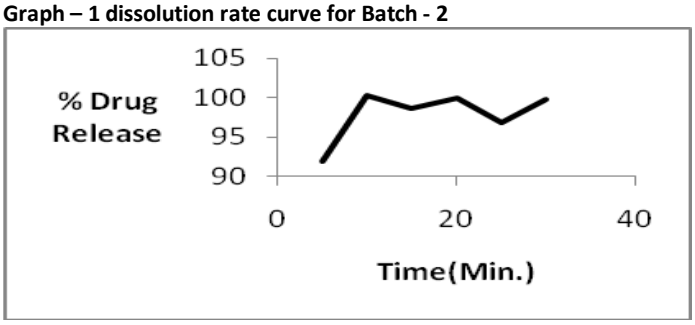
Time (min)	Cumulative % Drug Release		
	Controlled	After 15 days	After one months
0	0	0	0
10	92.99	90.62	88.38
20	95.83	95.89	94.61
30	99.82	98.39	98.06
40	100.67	99.49	99.13
50	101.23	100.69	100.29

Table 5: Stability study of in-vitro dissolution for formulation batch-2 stored at room temperature:

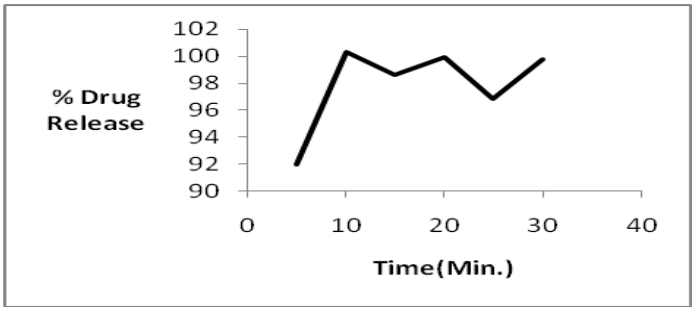
Dissolution rate curve for Metronidazole tablets:



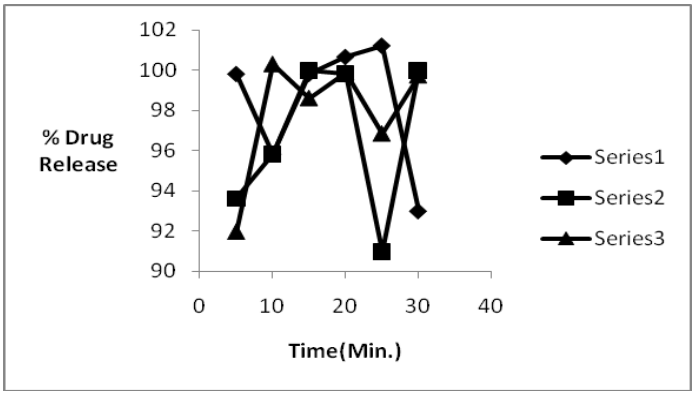
Graph – 1 dissolution rate curve for Batch - 2



Graph – 2 dissolution rate curve for Batch - 3



Graph – 3 dissolution rate curve for Batch - 4



Comparison of dissolution profile of Batch 2, 3, and 4: –

Discussion:

Preformulation Study:

In the preformulation study Metronidazole was characterized for bulk, tapped density and angle of repose. Results of the compressibility index, Hauser's ratio and angle of repose show that the all material has sufficient compressibility and flow properties.

Analytical Method

Analytical method suitable to determine the contents of Metronidazole was done by UV Spectroscopically. Metronidazole shows the absorption maxima at 253 nm in 0.1M HCl (pH 1.2) and absorption was linear through 1µg/ml to 10µg/ml. This method was found to be accurate, precise and specific for Metronidazole.

Selection of Tabletting Methodology

Effervescent method, Superdisintegrants addition method and Sublimation method were tried for formulation of film coated tablets by wet granulation technique. Super disintegration addition method exhibits the lowest disintegration time, hence it was concluded as the best method than compare to remaining methods.

Discussion of the characterization of the film coated tablets of metronidazole with various super disintegrants Sodium Lauryl sulfate and Croscarmellose sodium were tried for formulation of Film coated tablets. The concentration of superdisintegrant was taken 5, 20 .

Evaluation of powder blend:

a) Angle of Repose (θ)

The angle of repose for the entire formulations blend was found to be in the range 23.49° to 31.45°.

b) Compressibility Index

Compressibility index was found to be in the range 11.86 % to 19.18 %. All formulations showed good flow properties.

c) Hausner ratio

Hausner ratio was found to be in the range 1.13 to 1.23 and that indicated that all formulation has good flow properties.

Physical Parameter

a) Weight variation

All the formulated (Batch-2 to Batch-4 accept Batch-1) tablets were passed weight variation test as the % weight variation was within the IP limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values. The prepared formulation complies with the weight variation test.

b) Thickness

The maximum thickness of the formulation was found to be 5.1 mm. The minimum thickness of the formulation was found to be 4.7 mm. The average thickness of the all formulation was found to be 4.9 mm.

c) Hardness

The hardness of the tablet was found to be 1.0 to 3.2 Kg/cm^2. Batch-1 was failed in hardness and the other batch-2 to batch-4 were passed.

d) Friability test

The maximum friability of the formulation was found to be 0.31%. The minimum friability of the formulation was found to be 0.19%. The % friability was less than 1% in all the formulations accept batch-1 ensuring that the tablets were mechanically stable.

e) Drug content

The maximum drug content for the all formulation was found to be 101.05% and minimum % drug content from the all formulation was found to be 90.98%. The results were within the limit specified by the IP.

f) In vitro Disintegration test

In vitro Disintegration time was found to be in the range. From all formulations, Batch-1 (used SLS) has minimum disintegration time. Formulations containing croscarmellose sodium has taken more time for disintegration because of its gelling properties.

g) In vitro drug release

All the 4 formulations were subjected to in vitro dissolution studies by using 0.1M HCl. Dissolution data shows that formulation Batch-2 shows improved dissolution rate as compared to other formulations.

Comparison of formulated tablet with marketed tablet

In vitro dissolution study was carried out for conventional marketed (IDPL) Metronidazole tablet (Compeba) and compared with best formulation Batch-2 (Croscarmellose sodium). Batch-2 had taken 101.23% dissolution rate while Compeba taken 100.32% dissolution rate.

Stability Study

Stability study was carried out for the optimized formulation according to ICH guide lines at 2–8° C (controlled sample), Room temperature and 40° C for 1 month. The results showed that there was no significant change in physical and chemical parameter of the tablet, hence the formulation was found to be stable.

Conclusion:

Through the research work we can investigate a new drug delivery system by which the drug release at controlled rate with high dissolution rate which is very useful for patient. Both the derivatives Methyl Chloride and Isopropyl Alcohol have excellent film forming and coating properties. Large amount of SLS occur a problem of capping whereas small amount of SLS decreases disintegration time. Because SLS is a Superdisintegrant. By using MCC at the place of lactose & sugar we can decrease the tablet cost and increase dissolution rate. The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets. By using CCS in lubrication we can increase the dissolution rate of tablet because CCS helps to dissolve the tablet rapidly from edge and centre of the tablet. Large amount of binder like as starch, gelatin, glucose and polyvinylpyrrolidone (PVP) in paste prevent to the tablet from capping. No significant changes were observed when drug content were analyzed after one month stability testing.

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