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A STUDY ON DEVELOPMENT METHODS OF METRONIDAZOLE TABLETS IN OPTIMIZE ITS EFFECTIVENESS FOR COLON- RELEASE ACTIVITY

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ABSTRACT

In the present investigation two different polymers are used for the preparation of sustained release tablets HPMCK15M guar gum xanthan gum and Ethyl cellulose are selected Uniformity of weight hardness, friability and assay of all the prepared 8 formulations were found within the official and fixed limits. Drug release studies were performed with the help of *in vitro* dissolution based on the dissolution data the best formulation was selected Colon release tablets of Metranidazole increases the therapeutic efficacy of the drug.

KEYWORDS

HPMCK15M, Guar gum, Xanthan gum, Ethyl cellulose are selected, Uniformity of weight, Hardness, Friability and Metranidazole.

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INTRODUCTION

Ulcerative colitis, if not treated, leads to colon cancer. Cancer of the large intestine accounts for about 15% of cancer death in India. The mainstay of treatment for colon cancer is still surgery. In most cases, partial colectomy (removal of the part of the colon) is performed followed by chemotherapy[1].

(e.g. irritable bowel syndrome, ulcerative colitis, crohn's disease etc), infectious disease (amoebiasis) and colon cancer are failing as the drug do not reach the site of action in appropriate concentration. Thus

an effective and safe therapy of these colonic disorders, using site-specific drug delivery system is a challenging task to the pharmaceutical technologist.

MATERIAL AND METHODS

Preparation of Metronidazole matrix tablets

Lactose is used as diluent and a mixture of talc and magnesium stearate was used as lubricant. Natural and synthetic polymers such as guar gum, xanthan gum, hydroxyl propyl methyl cellulose, Ethyl cellulose were sieved separately and mixed with the drug and the other excipients. The powders were blended and granulated with 10% starch paste. The wet mass is passed through a mesh (16) and the granules were dried at 50^{o}C for 2 hrs. The dried granules were passed through a mesh (22) and these granules were lubricated with a mixture of talc and magnesium stearate.

Formulations of various batches of metronidazole tablets

Preformulation studies: Calibration curve

The drug was analysed by following UV Spectrophotometric analysis.

Procedure

Standard stock solution of metronidazole was prepared by dissolving 100mg of drug in 0.1N HCL and make up to 100ml in a standard volumetric flask with the same in order to get a concentration of 1mg/ml. From this solution a series of dilutions ranging from 1to 20µg/ml was prepared using 0.1 N HCL. The absorbance of each of the above dilutions was measured at a λmax of 282 nm against the blank. The method obeys the Beer's law in the concentration range of 20 to 140µg/ml.

From the obtained values a graph was plotted by taking concentration on x-axis and absorbance on y-axis .The value are shown in table and calibration curve was plotted.

Drugs-excipient compatibility study

The drug and the excipients chosen for the formulation were screened for compatibility study.

Compatibility study using FT-IR

Drug and excipients interaction was checked by comparing the FT-IR spectra of pure drug Metronidazole and FT-IR spectra of the physical mixture of drug and excipients. The IR spectra were taken from FT-IR-8400S (Shimadzu corporation, Tokyo, Japan). In the present study, potassium bromide (KBr) pellet method was employed. The samples were thoroughly blended with dry powdered KBr crystals. The mixture was compressed to form a disc. The disc was placed in the IR Spectrophotometer and the spectrum was recorded.

Pre compression studies

Drug properties like flow ability (angle of repose), bulk density, tapped bulk density, Carr's index are studied by following methods.

Angle of Repose

The flow ability is studied by angle of repose measurements. Angle of repose has been used as an indirect method qualifying powder flow ability, because of their relationship with their inter particle cohesion. A static heap of powder will be begin to slide when the angle of inclination is below that required to overcome cohesion i.e. Sliding occurs until the gravitational forces balance the inter particle forces. The balance of forces cause the powder poured from a container onto a horizontal surface to form a conical heap. The slide of the heap formed in this way makes an angle with the horizontal which is called the angle of repose represented by θ. It is given by,

$\theta = \tan^{-1}(h/r)$

Bulk Density

Bulk density is a characteristic of powder and is given by the mass 'm' of the powder occupying known volume 'V' according to the relation ship

Bulk density (ρ) = weight of powder/bulk volume of powder

The bulk density of powder depends primarily on particle size distribution, particle shape and tendency of particle to adhere to one another. The bulk density of powder is always less than the true density of its component particles, because the powder contains inter particle pores or voids

Tapped Density

If a particulate matter is poured into a cylinder which than tapped from a small height on to the

bunch several times the volume would likely decrease from the original which is referred as tapped density.

$$\text{Tap density:} \quad \frac{\text{weight of powder}}{\text{Tap volume of powder}}$$

Compressibility Index

This is an indirect method of measuring powder flow from bulk densities which was developed by 'Carr', the percentage compressibility of a powder is given by the equation

Where,

$$\text{CARR'S Index} = \frac{\text{Bulk density-Tap density}}{\text{Tap density}} \times 100$$

The standard values are given in the table.

Preformulation Studies

Preparation of mono basic potassium Phosphate (0.2M)

Dissolve 27.22g of mono basic potassium phosphate in water and dilute with water to 1000ml.

Preparation of 6.8 phosphate buffer

Place 50ml of mono basic potassium phosphate solution in a 200ml volumetric flask, add 22.4ml of 0.2 M NAOH solution, then add water to make the required volume.

Preparation of 7.2 phosphate buffer

Place 50ml of monobasic potassium phosphate solution in a 200ml volumetric flask, add 34.7ml of 0.2m NAOH solution, then add water to volume.

Evaluation Studies

The punched tablets were stored in a suitable container and subjected to the following evaluation tests:

Drug content
Weight variation
Hardness
Friability
In vitro drug release studies

Drug Content (mg/ml)

500mg of tablet formulation was placed in 100 volumetric flask, add methanol (1or2ml) and make up the volume to 100ml with 6.8 phosphate buffer and keep a side for 24 hours, then solution was filtered using whatmann filter paper. Measure the absorbance of the filtrate at 282nm by using UV Visible spectrophotometer. Amount of drug in each formulation was calculation by using the formula.

$$\text{Drug content} = \frac{\text{concentration} \times \text{dilution factor} \times 100}{1000}$$

Weight Variation

In this test first average weight of 20 tablets was calculated and then the individual weight of each tablet was found. The percentage derivation from the average of each tablet was calculated according to the formula.

$$\%\ \text{derivation} = \frac{\text{Individual weight of tablets} - \text{average weight of tablet} \times 100}{\text{Individual weight of tablet}}$$

If the value obtained is positive it is called as positive deviation and if the value is negative it is called as negative deviation. The data is presented in table.

According to I.P. Permissible percentage weight variation for uncoated tablets

The values obtained upon carrying out the test on the tablets are mentioned in the tablet:

Hardness

The hardness of the tablet is tested by using Monsanto Hardness tester.

The hardness is adjusted to 4kg/cm^2 before the punching of the tablet itself. However in order to know the exact values the test was conducted by taking 20 tablets. The average value was calculated from the individuals.

Friability

This is a test to know the manufacturing problems like chipping, cracking etc. in this test certain number of tablets whose weight is equivalent to 5gm were taken and their total weight was noted. Then these tablets were kept in the friability apparatus which is rotated at 25rpm. It was made to make 100 revolutions. Then again the total weight of the tablets was noted and the percentage friability was calculated using this formula.

$$\%\text{Friability} = \frac{\text{Weight before friabilation} - \text{Weight after friabilation} \times 100}{\text{Weight before friabilation}}$$

Rate of Drug Release

For these studies the dissolution studies are done. The apparatus used is the I.P. dissolution apparatus-II. In this 900ml of distilled water at 37^o $\pm$1 temperature (dissolution fluid medium) was used and then the tablet was placed and the paddle was made to make 50rpm. The 5ml samples were

collected up to 8 hours with interval of 1 hour. The collected samples were subjected to chemical treatment and thus the optical densities were known using spectrophotometer at a lamda max of 282nm. From the calibration curve the concentration was calculated and interpreted for the drug release characteristics. The studies were conducted twice and the average values were considered. In order to know the order of drug release a graph was plotted between % drug release vs time.

Accelerated Stability studies

For all the pharmaceutical dosage forms it is important to determine the stability of the dosage form this will include storage at exaggerated temperature conditions, with necessary extrapolations to ensure the product will, over its designed shelf life, provide medication for absorption at the same rate as when originally formulated. The metronidazole tablets of the best formulation are tested for stability for 3 months in accelerated test conditions. The tablets are exposed to 40^{o} $\pm 2^{o}$C and 75±5% RH conditions for 3 months. The tablets are observed for change in physical appearance, moisture content, assay values, impurities and dissolution values at end of first second and third month. Stability was determined.

Release kinetics

The results of *In-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

Log cumulative percent drug remaining versus time (first order kinetic model)

Cumulative percent drug release versus square root of time (Higuchi's model)

Cumulative percent drug release versus time (zero order kinetic model)

Log cumulative Percent Drug released versus log time (Korsmeyers model)

Drug release kinetics-model fitting of the dissolution data

Whenever a new solid dosage form is developed or produced, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, Higuchi, Korsmeyers-Peppas models. Other release parameters, such as dissolution time (tx%), dissolution efficacy (ED), difference factor (f1), similarity factor (f2) can be used to characterize drug dissolution / release profile.

Zero-order kinetics

A zero-order release would be predicted by the following equation.

At = Ao - Kot

Where, At = Drug release at time t Ao = Initial drug concentration

K_O = Zero-order rate constant

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to K_O.

Use

This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

First-order kinetics

A first order release would be predicted by the following equation. Log C = Log C_O - Kt / 2.303

Where C = Amount of drug remained at time t C_O = Initial amount of drug

K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant K can be obtained by multiplying 2.303 with slope values.

Use

The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is

proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes.

Higuchi model

A form of the Higuchi Square Root Law is given by equation:

$Q = Ks \sqrt{t}$ Where

Q = Amount of drug dissolved at time t Ks = Higuchi rate constant

The Higuchi square root equation describes the release from systems where the solid drug is dispersed in an insoluble matrix, and the rate of drug release is related to the rate of drug diffusion.

Korsmeyer and peppas release model

In order to understand the mode of release of drug from swell able matrices, the data were fitted to the following equation,

$Mt / M\infty = Kt^n$

Where,

Mt / Mά = Fraction of drug released at time 't'

K = Constant incorporating the structural and geometrical characteristics of the drug/polymer system.

n = Diffusion exponent related to the mechanism of release.

$Log\ Mt / M\infty = Log\ K + n\ Log\ t$

The value of n for a cylinder is <0.45 for Fickian release, > 0.45 and < 0.89 for Non-Fickian release, 0.89 for the case 2 release and > 0.89 for super case 2 type release.

Table No.1: Formulation of matrix tablets (Quantity of tablets in mg)

S.No	Ingredient	F1	F2	F3	F4	F5	F6	F7	F8
1	Metronidazole	200	200	200	200	200	200	200	200
2	Guar gum	80	-	-	-	100	-	-	-
3	Xanthum gum	-	80	-	-	-	100	-	-
4	HPMC	-	-	80	-	-	-	100	-
5	Ethyl cellulose	-	-	-	80	-	-	-	100
6	Lactose	155	155	155	155	135	135	135	135
7	Starch paste	50	50	50	50	50	50	50	50
8	Talc	10	10	10	10	10	10	10	10
9	Magnesium stearate	5	5	5	5	5	5	5	5

Table No.2: Angle of Repose

S.No	Angle of Repose (Degrees)	Flowability
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>50	Very poor

Table No.3: Carr'sindex

S.No	Carr's Index (%)	Flowability
1	5-15	Excellent
2	12-16	Good
3	18-21	Fair to passable
4	23-35	Poor
5	33-38	Very Poor
6	>40	Very Very Poor

Table No.4: Weight Variation

S.No	Tablet Weight	%Weight Variation
1	<130	10
2	130-324	7.5
3	>324	5

RESULTS AND DISCUSSION

Table No.5: Calibration curve of metronidazole

S.No	Concentration(µg/ml)	Absorbance
1	20	0.205
2	40	0.379
3	60	0.542
4	80	0.691
5	100	0.835
6	120	0.979

Table No.6: Evaluation of Granules

Formulation	Bulk Density (Kg/Cc)	Tapped Density (Kg/Cc)	Angle of Repose	Carr'S Index (%)
F1	0467	0.420	25.31	10.72
F2	0.472	0.422	24. 51	11.75
F3	0.603	0.548	26.32	9.85
F4	0.572	0.517	27. 51	10.55
F5	0.505	0.450	25.62	10.75
F6	0.404	0.361	25. 13	11.85
F7	0.602	0.533	25. 61	12.75
F8	0.551	0.498	25. 63	10.61

Table No.7: Evaluations of Tablets

Formulations	Weight Variation	% Friabiliy	Hardness(Kg/ Cm^2)	%Drug Content (Mg/Ml)
F1	495	8	4.9	96.43
F2	495	6	5.1	98.71
F3	495	7	4.9	97.53
F4	498	6	5.8	98.25
F5	505	8	5	99.34
F6	503	8	4.8	95.80
F7	498	6	5.5	97.37
F8	495	7	5	99.58

In vitro Dissolution Studies

Table No.8: Percentage drug release

Time (Hrs)	F1	F2	F3	F4	F5	F6	F7	F8
1	11.31	7.85	20.83	12.56	14.12	15.81	15.35	14.52
2	23.72	10.92	36.56	27.07	25.17	29.31	23.82	25.57
3	31.05	29.56	50.28	42.71	33.23	35.82	31.46	31.68
4	41.5	36.47	66.52	54.65	41.30	40.91	45.51	42.15
5	54.52	45.37	70.15	57.11	56.29	51.13	50.93	51.36
6	60.65	60.26	81.17	61.61	68.31	58.41	62.27	62.57
8	71.08	71.35	92.58	76.15	71.53	61.57	73.38	70.73
10	83.08	82.09	99.07	80.56	75.35	71.85	89.58	80.67
11	88.01	87.54	-	83.52	79.33	75.61	94.37	85.41
12	91.65	89.35	-	87.15	83.15	83.15	98.13	89.31

Table No.9: Determination of Release Kinetics

Time	Square root of time	Log time	Cum % drug release	Log cumulative% drug release	Cum% drug remaining	Log Cum% drug remaining
1	1.000	0.000	15.35	1.186	84.65	1.928
2	1.414	0.301	23.82	1.377	76.18	1.882
3	1.732	0.477	31.46	1.498	68.54	1.836
4	2.000	0.602	45.51	1.658	54.49	1.736
5	2.236	0.699	50.93	1.707	49.07	1.691
6	2.449	0.778	62.27	1.794	37.73	1.577
7	2.646	0.845	73.38	1.866	26.62	1.425
8	2.828	0.903	89.58	1.952	10.42	1.018
10	3.000	0.954	94.37	1.975	5.63	0.751

Table No.10: Accelerated Stability study for the Optimized formulation

S.No	Test	Initial	Period in months		
			1	2	3
1	Physical appearance	White color, flat	White color, flat	White color, flat	White color, flat
2	Weight Variation (mg)	200±1.6	200±1.6	200±1.6	200±1.6
3	Hardness(kg/cm2)	5.5± 0.24	5.5±0.32	5.5±0.38	5.5±0.41
4	Friability (%)	0.22±0.14	0.22±0.15	0.22±0.15	0.22±0.16
5	*In vitro* release (%)	89.24±0.7	89.24±0.9	88±0.7	86±0.8

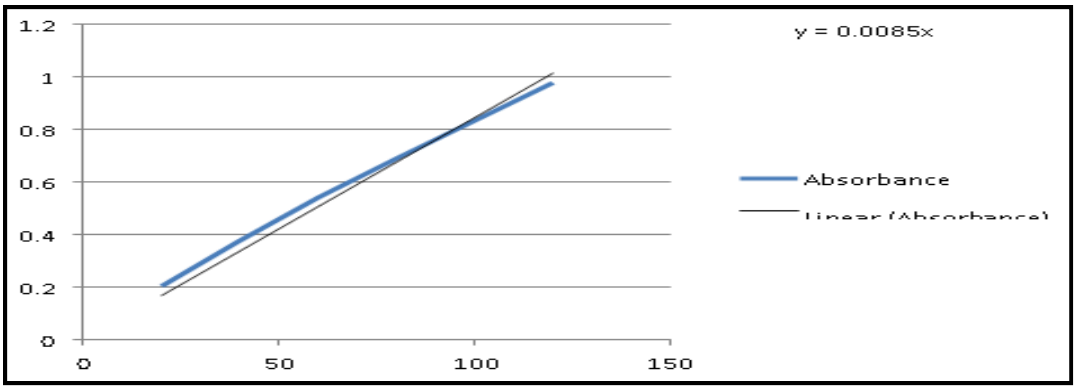

Figure No.1: Calibration curve of metronidazole

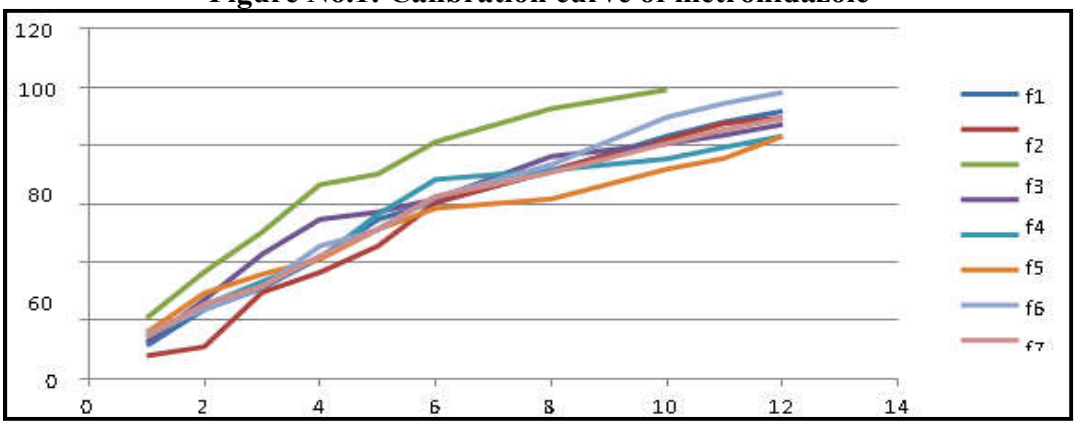

Figure No.2: *In vitro* dissolution profile of different formulations (F1-F8)

SUMMARY AND CONCLUSION

The difficulties faced by conventional dosage forms are successfully overcome by the design of controlled and sustained release dosage forms over a period of time however benefits of these technologies. The present investigation is on sustained release tablets of Metranidazole has been studied.

In the present investigation two different polymers are used for the preparation of sustained release tablets, HPMCK15M, guar gum, xanthan gum and Ethyl cellulose are selected.

Uniformity of weight, hardness, friability and % assay of all the prepared 8 formulations were found within the official and fixed limits.

Drug release studies were performed with the help of *in vitro* dissolution, based on the dissolution data the best formulation was selected. Colon release tablets of Metranidazole increases the therapeutic efficacy of the drug.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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