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Research Article

pH Dependent Release Potential of Natural Polymers in Sustained Release of Ornidazole From Colon Targeted Delivery System

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ABSTRACT

The aim of present work was to prepare colon specific delivery system of Ornidazole using different ratio of shellac, zein and guar gum. From study of various literature it revealed that shellac, zein and guar gum released drug from dosage form at the pH of 6.9, 11.5, 7-9 respectively. The main problem associated with colon targeted drug delivery system is degradation of drug in the acidic environment of stomach to circumvent the present problem different combinations of shellac, zein and guar gum were employed in the formulation of colon targeted tablet. Several preformulation parameters were determined such as melting point, FTIR spectroscopy, preparation of calibration curve, determination of λ_{max} and partition coefficient. After the preformulation studies, next steps were preparation of core tablets, evaluation of core of tablets and coating of tablets. The data obtained from preformulation study seven formulations were developed and evaluated for various parameters. Based on evaluated parameter such as weight variation, friability, dissolution study, in-vitro drug release etc. the F7 formulation show better results colon targeted tablets. Drug content in F7 formulation was 95% and drug release after 6 hrs was 96%. Formulation containing combination of shellac, zein and guar gum released least amount of drug in the acidic environment of stomach and released most of the drug in colon. It is evident from above discussion that targeted delivery to colon will result in lesser side effects and maximum utilization of drug.

Keywords: Ornidazole, Shellac, Zein, Guar Gum, Colon, Crohn's disease.

INTRODUCTION

Over the past two decades, the pharmaceutical market has been demonstrated increasing day by day for modified and targeted drug delivery system. These systems have been centred on constant, variable; sustain drug release targeting the therapeutic agent to a specific site/tissue/organ. However, recently there is certain phenomenon for which such release pattern is not suitable. Such phenomenon that lead to the requirements of a time programmed therapeutic system, which are capable of releasing drug after predetermined time delay and maintain constant drug levels throughout the day[1,2]. Co-ordinate with the drug release to the body's circadian rhythms have been fundamental strategies involves for selecting a new drug delivery system which increase the efficacy and safety of drugs, according to proportion of their peak plasma concentrations during the 24 hours in synchrony with biological rhythm. The recent literature show a variety of chronotherapeutic drug delivery systems, which have been recognized as potentially beneficial to the chronotherapy of severe chronic diseases that display time-dependent symptoms such as ulcers, asthma and cardiovascular disease. Such chronotherapeutic drug delivery system controls drug release pattern according to circadian rhythms and the timing of symptoms[3,4,5].

Diseases intended to be treated when colon drug targeting is adopted are ulcerative colitis, Crohn's disease (chronic inflammation of the digestive tract, especially of the lower small intestine and colon, which may develop thick scars) /irritable bowel disease, carcinomas/colorectal cancer, amoebiasis and other colonic infections.

Single unit dosage forms are formulated as enteric coated tablets with extended release polymers, coated with pH dependent polymers. When the coating dissolves in the upper intestine, the core tablet releases the drug in a sustained manner in the colon. A number of single unit dosage forms make multiple unit dosage forms, in the form of tablet, granules or microspheres, enclosed within a capsule or tablet. When the tablet or capsule disperses to release its contents, each of the particulates behaves as single unit dosage form[6]. Ornidazole is a drug that cures some protozoan infections. Ornidazole is widely used in Crohn's disease after bowel rejection.

Ornidazole is a nitro imidazole which has broad spectrum cidal activity against protozoa and some anaerobic bacteria. Its selective toxicity to anaerobic microbes involves: 1. Drug enters the cell by diffusion, 2. In anaerobic organisms redox proteins are present, these proteins reduce the nitro group of drugs. So, only reactive nitro radicals which exerts cytotoxic action by damaging DNA and other critical biomolecules, 3. DNA helix destabilization &strand breakage has been observed.

MATERIALS AND METHODS

Ornidazole, guar gum, shellac, zein, micro crystalline cellulose (MCC) & PVP-K30 were provided by the

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Table 1: Composition of Ornidazole tablet & tablet coating polymers.

S. No.	Ingredients	F1	F2	F3	F4	F5	F6	F7
1	Ornidazole	200	200	200	200	200	200	200
2	PVP	30	30	30	30	30	30	30
3	Microcrystalline cellulose	30	30	30	30	30	30	30
4	Starch	10	10	10	10	10	10	10
5	Talc	10	10	10	10	10	10	10
6	Magnesium Stearate	15	15	15	15	15	15	15
7	Solvent	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Total weight of tablets before coating		300 mg	300 mg	300 mg	300 mg	300 mg	300 mg	300 mg
Coating material		CM1	CM2	CM3	CM4	CM5	CM6	CM7
1	Shellac	200	0	0	100	100	0	66.66
2	Guar gum	0	200	0	100	0	100	66.66
3	Zein	0	0	200	0	100	100	66.66
Total weight of tablets after coating		500 mg	500 mg	500 mg	500 mg	500 mg	500 mg	500 mg

Table 2: The percentage deviation in the weight variation is shown.

Average weight of a tablet	% deviation
130mg or less	10
Mere then 130mg & less then 324mg	7.5
324mg or more	5

Table 3: Dissolution studies *in-vitro.*

Parameter	Specification
Dissolution medium	900 ml 0.1 N HCl for first 2 h then replaced with 6.8 pH phosphate buffer and continued for 24 h
Temperature	37ºC ± 5ºC
Rotation Speed	50 rpm
Volume Withdrawn	5 ml
λ_{max}	277 nm
Tablet Taken	1 tablet

Table 4: Organoleptic properties of Ornidazole.

Parameter	Drug
Colour	Darkened urine
Odour	Odorless
Taste	Tasteless complex
Appearance	White powder

Table 5: Solubility of Ornidazole.

Solvent system	Solubility (mg/ml)
Water	17.305
Ethanol (95%)	705

research center of S.O.S. pharmaceutical science, Jiwaji University, Gwalior, India. All other chemicals and ingredients were used for study, were of Analytical grade.

Preformulation studies

The drug was identified by various evaluation parameters such as physical appearance, solubility, UV spectral analysis, IR Spectral analysis etc.

Melting Point

Melting point of the drug was determined by taking a small amount of drug in a capillary tube closed at one end and it was placed in melting point apparatus and the temperature at which the drug melts was note. Average of triplicate readings was taken.

Solubility

Solubility study of Ornidazole was carried out using saturation method it is freely soluble in ethanol (95%) and sparingly soluble in water.

Partition coefficient

Mixture of 50 ml water and 50 ml benzene was taken in a separating funnel. 100 mg of drug was added to mixture. Mixture was shaken, and set aside for half an hour. Both phases were separated. Concentration of drug of each layer was determined by UV spectrophotometer.

Determination of λ_{max}

The standard stock solutions of Ornidazole were prepared separately, by dissolving 100 mg of Ornidazole in 100 ml of three different dissolution media. A stock solution of Ornidazole was further diluted with respective media in different ratio to get a standard solution of concentration 100 µg/ml[7].

Preparation of calibration curve

The standard solution of Ornidazole (2,4,6,8,10,12,14,16,18,20 µg/ml) in phosphate buffer 7.4 pH were prepared and scanned in the entire UV range to determine the λ_{max} of drugs. The λ_{max} of Ornidazole was found to be 277 nm at the 7.4 pH of phosphate buffers solution. The absorbance of Ornidazole standard solutions were taken at λ_{max} in respective media, and calibration curves were plotted at these wavelengths.

FTIR spectroscopy

FTIR studies were performed to determine the chemical interaction between the drug and Excipients used in the formulation.

Preparation of granules

In wet granulation, a liquid binder or an adhesive is first added to the powder mixture. The wetted clump is then passed through a screen of the reported mesh size, and resulting granules were dried. The dried granules were passed through a second screen of a smaller mesh to reduce the size of the granules and for provide uniformity. Over

Determination of Ornidazole λmax

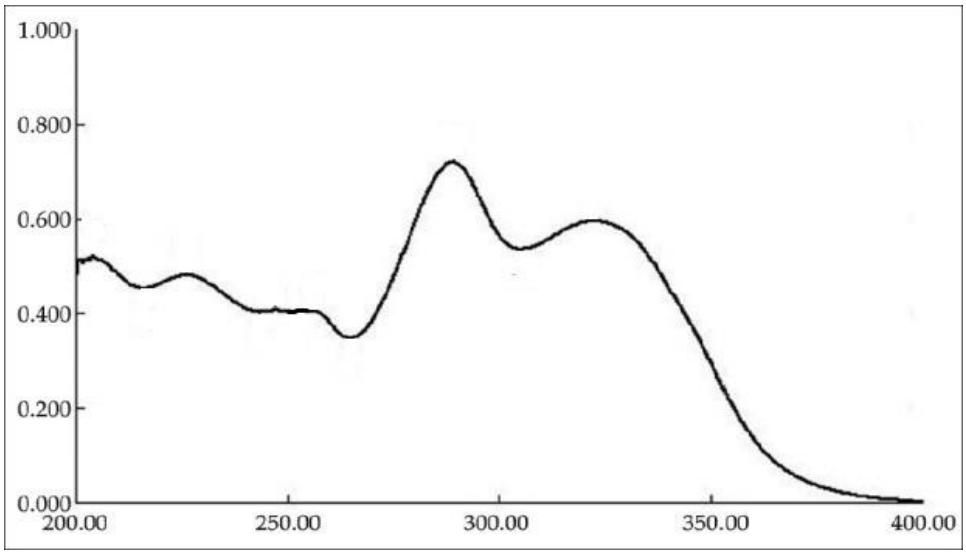

Figure 1: The λ_{max} of Ornidazole in 0.1 N HCl 277 nm.

Preparation of standard calibration curve

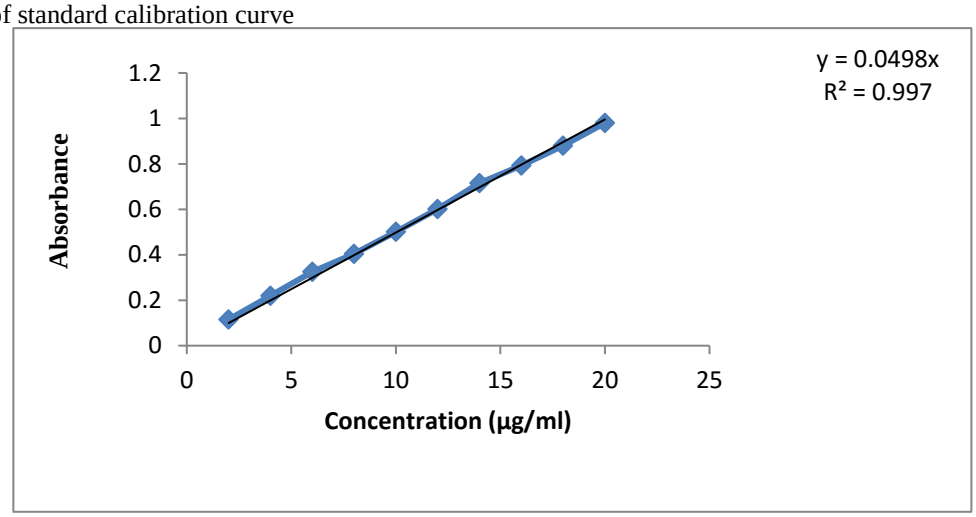

Figure 2: Calibration curve of Ornidazole in phosphate buffer of pH- 7.4.

Table 6: Partition coefficients of Ornidazole

Ornidazole	Partition coefficients value	
	In water/ethanol	In benzene/phosphate buffer
	0.2415	0.5124

wetting usually results in granules that are too hard for proper tableting, while under wetting usually results in the preparation of tablets that are too soft and tend to crumble.

Evaluation of granules (Micromeritic property of granules)

Angle of repose

The surface of a pile of the powder and horizontal plane, form an angle and maximum angle possible between them is called angle of repose. The frictional force in a loose powder or granules can be measured by angle of repose[8].

$\tan\theta = h/r$

Where, θ is the angle of repose, h is the height of the pile; r is the radius of the base of pile.

Carr's index

It is also called the compressibility index. The flow ability of powder can be evaluate by compare the bulk density and tapped density of powder and the rate at which it pack down. Compressibility index is calculate by using formula[9,10].

Compressibility index (%) = $\frac{D_T - D_B}{D_T} \times 100$

Where, DT = Tapped density, DB = Bulk density

Hausner's ratio

It is the ratio of tapped density to bulk density. It is given by-

Hausner's ratio = D_T/D_B

Where, D_T = Tapped dens. D_B = Bulk density

Bulk density

It is the ratio of total mass of powder to the bulk volume of powder. The bulk density of powder depends mainly on particle size distribution, particle shape and the tendency of particle to adhere to one another. It is expressed in gm/cc and is given by-

$D_B = \frac{M}{VD}$

M = Mass of powder,

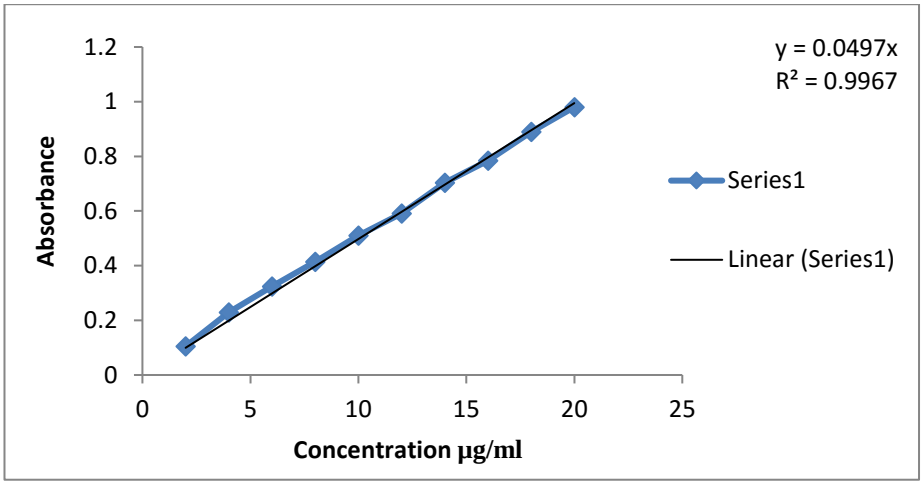

Figure 3: Calibration curve of Ornidazole in phosphate buffer of pH- 6.8.

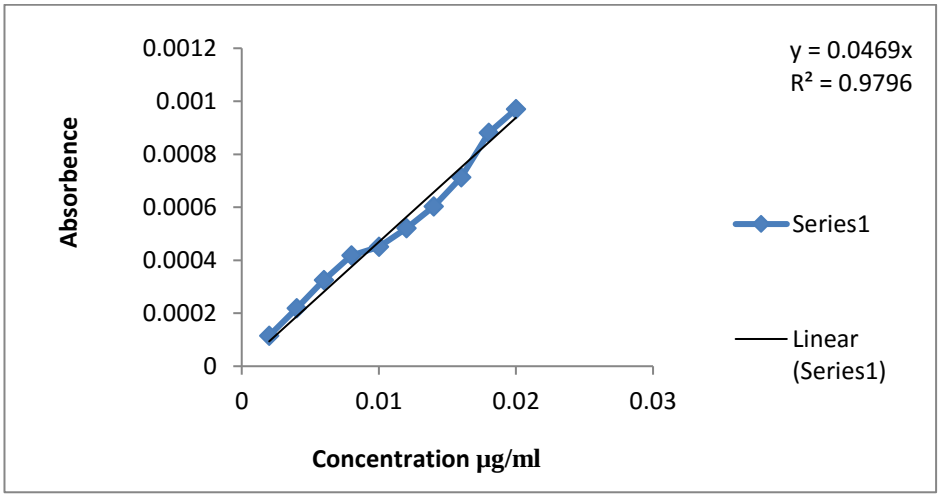

Figure 4: Calibration curve of Ornidazole in phosphate buffer of pH- 1.2.

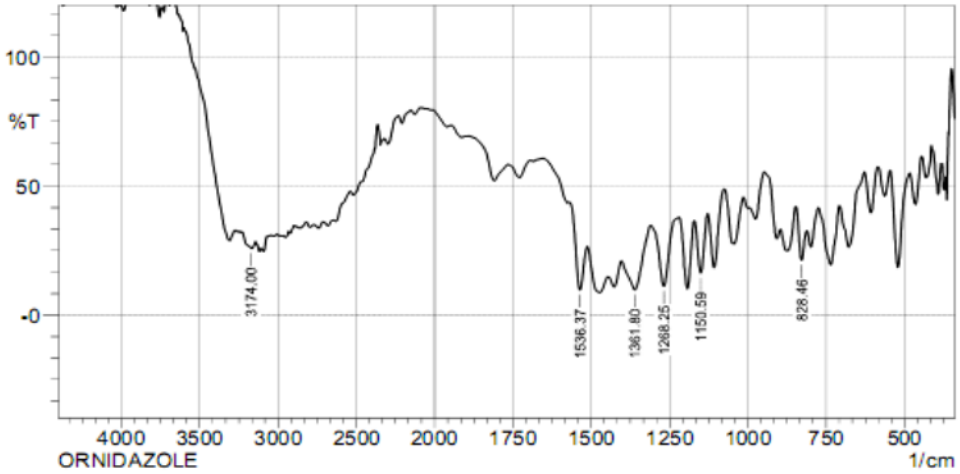

Figure 5: FTIR of Ornidazole

V_o= Bulk volume of powder

Tapped density

It is the ratio of total weight of powder to the tapped volume of powder. It is expressed in gm/cc and is given by-

$$D_T = \frac{M}{V_0}$$

Preparation of core tablets

A tablet is a pharmaceutical dosage form. Tablets may be defined as the solid unit dosage form of medicament or medicaments with or without suitable diluents and prepared either by molding or by compression.

Ingredients except glidants and lubricants were thoroughly mixed and passed through sieve no. 60. Granulation was done with 5% starch paste. The wet mass

Table 7: FTIR peak interpretation of Ornidazole.

Assignment	Reported Peak (cm-1)	Observed Peak (cm-1)
O-H stretching mode asymmetric	3174.1	3174.00
NO2 stretching mode	1536.9	1536.37
NO2 stretching mode symmetric	1361, 1269.5	1361.80, 1268.25
C-O stretching mode	1149	1150.59
C-N, N2 stretching mode	828	828.46

Table 8: Micromeritic properties of Ornidazole granules.

Ornidazole granules.							
Property	GF1	GF2	GF3	GF4	GF5	GF6	GF7
Angle of repose	21.35± 0.70	20.15± 0.35	22.10± 0.55	21.10± 0.69	22.16± 0.23	20.22± 0.67	22.06± 0.89
Bulk density	0.5± 0.011	0.51± 0.018	0.47± 0.020	0.52± 0.018	0.5± 0.012	0.51± 0.008	0.5± 0.0019
Tapped density	0.55± 0.008	0.56± 0.014	0.52± 0.014	0.54± 0.001	0.53± 0.009	0.55± 0.011	0.54± 0.007
Carr's index	9.09± 0.63	8.92± 0.44	9.61± 0.57	9.23± 0.28	8.99± 0.50	9.29± 0.73	9.18± 0.19
Hausner's ratio	1.100± 0.05	1.090± 0.09	1.106± 0.12	1.108± 0.08	1.800± 0.23	1.250± 0.14	1.100± 0.03
Flowability	Good	Good	Good	Good	Good	Good	Good

Table 9: Evaluation of Ornidazole tablets before polymer coating.

Formulation code							
Test parameters	F1	F2	F3	F4	F5	F6	F7
Hardness (kg/cm^2)	5.1±0.24	4.9±0.30	5.1±0.26	4.8±0.23	5.6±0.30	5.2±0.20	5.4±0.27
Diameter (in mm)	9.51±0.21	9.16±0.29	9.47±0.30	9.61±0.28	9.55±0.31	9.54±0.32	9.36±0.22
Thickness (in mm)	5.42±0.10	5.21±0.11	5.42±0.13	5.45±0.10	5.42±0.12	5.42±0.09	5.41±0.09
% Friability	0.457	0.512	0.465	0.575	0.412	0.551	0.451
Weight variation test	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Drug content*(mg)	95.59±1.5	94.79±1.6	95.21±1.4	95.51±1.8	95.04±1.5	95.68±1.4	95.78±1.1

was passed through sieve no. 12 and dried at 50˚C for 1 hr. weight variation, hardness, friability, tablet thickness and

Table 10: Evaluation of Ornidazole tablets after polymer coating.

Formulation code							
Test parameters	F1	F2	F3	F4	F5	F6	F7
Hardness* (kg/cm^2)	5.3±0.14	5.4±0.16	5.3±0.16	5.4±0.13	5.4±0.14	5.3±0.12	5.4±0.11
Diameter (in mm)	10.88±0.23	10.96±0.29	10.98±0.29	10.76±0.30	10.86±0.21	10.78±0.29	10.98±0.22
Thickness (in mm)	5.41±0.10	5.41±0.12	5.42±0.10	5.41±0.13	5.41±0.11	5.41±0.10	5.41±0.10
% Friability	0.567	0.532	0.565	0.565	0.423	0.550	0.565
Weight variation test	Passes	Passes	Passes	Passes	Passes	Passes	Passes
Drug content*(mg)	95.59±1.5	94.79±1.6	95.21±1.4	95.51±1.8	95.04±1.5	95.68±1.4	95.78±1.1

the dried granules were lubricated with Magnesium Stearate and talk then compressed in to tablet using single station punch machine[11].

Tablet coating

Dip coating method was used for coating of outer layer of tablets. 5% w/v solution of organic polymer in acetone was used for the coating. Shellac, Zein and Guar gum incorporated as natural coating polymer in different quantities. Titanium dioxide (0.05% w/w) used as opacifier and talc used as antiadherant, to prevent adhering of tablets during the coating process.

Evaluation of colonic tablets of Ornidazole

Physical characterization of tablet

All the seven batches of tablet formulations were characterized by official evaluation parameters such as data collected for further optimization and evaluation.

Weight variation

The tablets were selected randomly from each formulation and weight individually to check for weight variation. According to the official test, 20 tablets are generally weight individually and collectively. Average weight per tablet was calculated from the collective weight. Then the weight of individual tablet was compared with the average weight to determine weight variation. The U.S. pharmacopoeia allows a little variation in the weight of the tablet[12].

Hardness

Tablet requires, withstanding mechanical shock during the manufacturing, packaging and shipping. A tablet must show certain amount of strength or hardness for resistance to friability. The hardness of tablet was determined using

Table 11: *In vitro* drug release studies of the formulation.

Formulation	% Release						
Time(hr.)	F1	F2	F3	F4	F5	F6	F7
1	15.2±0.42	21.4±0.36	18.2±0.33	20.2±0.39	15.2±0.37	18.3±0.40	18.1±0.29
2	28.7±0.29	39.3±0.31	36.9±0.30	38.3±0.28	39.6±0.33	38.2±0.29	39.4±0.33
3	49.3±0.31	48.2±0.27	52.8±0.28	56.7±0.29	65.5±0.30	54.7±0.33	59.3±0.31
4	58.4±0.33	69.7±0.34	63.7±0.36	79.8±0.33	77.3±0.32	67.3±0.35	68.7±0.32
5	72.2±0.27	78.8±0.39	72.2±0.28	88.9±0.29	82.8±0.32	74.2±0.31	82.5±0.33
6	90.1±0.28	86.7±0.33	84.6±0.34	92.3±0.37	88.2±0.32	82.5±0.31	96.4±0.26

Monsanto hardness tester. The tablet was placed between both the punches of hardness tester and force was applied. The force at which the tablet was about to crush was noted. It was expressed in kg/cm^2. Three tablets are randomly pick from each formulation and the mean and standard deviation values are calculate[13].

Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of strength and lamination or breakage when subjected to mechanical shock or irritation. The friability of tablets was determined by using Roaches Friabilator. It is expressed in percentage (%). Ten tablets were initially weighted ($W_{initial}$) and transferred into friabilator. Weighted tablet sample is placed in the chamber and the friabilator was operated at 25 rpm for 4 min. or run up to 100 revolutions and drop the tablet from a height of 15 cm with each revolution. The tablets were weighted again (W_{final}). The percentage friability was then calculated by- % friability of the tablet less than 1% is considered acceptable.

Friability (%) = $W_{initial}$ - W_{final} / W_{final} x100

Uniformity of thickness

Vernier calliper provides the accurate measurements and information on the variation of tablet thickness. In another method, sliding calliper was used for measurement of tablet thickness; in this method, we put 5 or 10 tablets in holding tray so that we could measure the tablet thickness. Thickness should not deviate by ±5% from the standard thickness[14].

Drug content

Ten tablets from each batch were powdered and 100 mg (equivalent quantity) of drug content was dissolved in 6.8 pH phosphate buffer (100 ml). 10ml of filtrate was suitably diluted and analyzed for drug content by U.V. spectrophotometers at 277 nm[15].

Dissolution studies

Dissolution studies were carried out using tablet USP II dissolution test apparatus. Main purpose of *in vitro* dissolution study was;

Up to 100% drug release from the tablets.

Uniform and constant rates of drug release from batch and should be same as the release rate from those proven to be bioavilable and clinically effective[10,16].

In vitro drug release studies

In vitro studies were carried out using a USP type II dissolution apparatus. The tablet was placed in 900ml of 0.1N HCl at paddle speed of 50 rpm maintained at 37°C±0.5°C for 2 hrs. 5 ml of Sample was taken and analyzed using UV spectrophotometer at 277 nm. Then the dissolution medium was replaced with pH 6.8 phosphate buffer (900 ml) and tested for drug release for 24 hr at same temperature and same rotation speed.

RESULTS AND DISCUSSION

Identification of drug

Melting Point

The melting point was found to be in the range of 77-78ºC which is in good agreement with the reported values.

Solubility

Solubility study of Ornidazole was carried out using saturation method it is freely soluble in ethanol (95%) and sparingly soluble in water.

Partition Coefficient

Partition coefficient of Ornidazole was carried out in distilled Water/ethanol and Benzene/phosphate buffer result are 0.2415 and 0.5124 which shows drug are hydrophilic in nature.

FTIR Spectroscopy

FTIR was performed on Ornidazole, PVA and solid dispersion of Ornidazole with all carriers. The IR spectra (Figure 5) showed all the principal IR absorption peak of Ornidazole at 3174.00 cm-1, 1536.37 cm-1, 1361.80 cm-1, 1268.25 cm-1, 1150.59 cm-1, 828cm-1. FTIR of formulations of drug and polymers used in studies shows that all the peaks of drug, polymer as it is, and drug is present in free form. This indicates that there is no Chemical interaction in between Ornidazole and the polymers employed in formulations.

Micromeritic properties of Ornidazole granules

Angle of repose, Bulk Density and Tapped Density

The formulation shown in table, which shows free flowing nature of form granules of all.

Hausner's ratio

Hausner's ratio is an indirect index of ease of powder flow upon considering the Micromeritic properties of all formulation, formulation GF3 of granules had best flow properties of my products.

Carr's index

Carr's index from 8.92-9.61%. Formulation GF3 of granules had lowest Carr's index indicating excellent compressibility.

Formulation and In-vitro evaluation of Ornidazole colon targeted tablets

The Ornidazole tablet formulations were prepared successfully by wet granulation method and coating polymer combination of shellac, guar gum and zein in different proportions was used (F1 to F7) as coating and forming polymers (The composition of the Ornidazole tablet formulations were shown in Table 1).

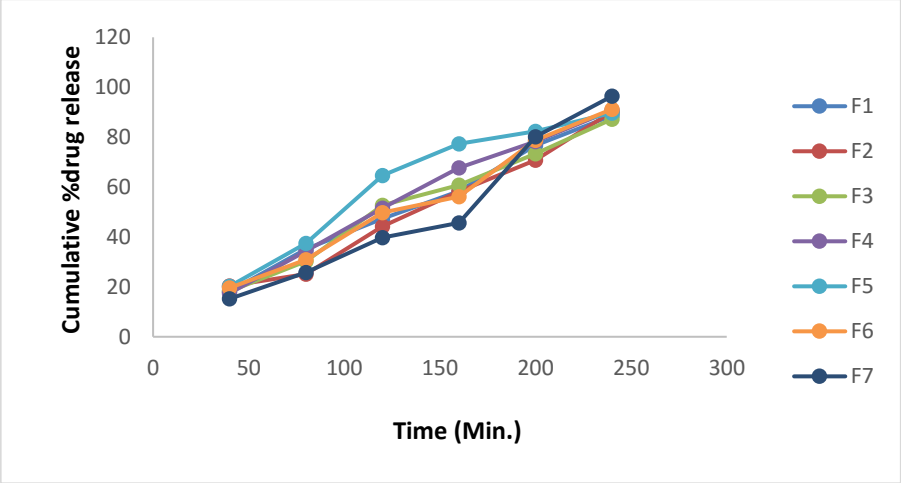

Figure 6: *In vitro* drug release in colon.

Drug dissolution profiles determination by various kinetics models

The data obtained from in vitro release study were fitted in to various kinetic models. As a result of Correlation coefficients F7 formulation showed higher correlation with zero order kinetic plots and Higuchi showed first order kinetic. So, on the basis of results we can say that, drug release mechanism was controlled release.

In vitro drug release Studies

In vitro drug release study was performed by buffer change method as like the GI environment and the drug release study was continued for 6 hours for all formulations in order to check the variation in drug release pattern. *In vitro* dissolution data were fitted into various kinetic models such as Higuchi's model, zero order and first order for study of drug release kinetics and mechanism of drug release. The tablet formulations were studied to know *in vitro* drug release rate in 0.1 HCL (pH 1.2) for 2 hrs. The formulation capability checked to withstand in physiological environment of the stomach and small intestine. The Ornidazole enteric coated tablets optimized formulation F7 shows desired drug release 96.4±0.26% after 6 hrs as it is composed of equal amount of shellac, zein and guar gum (66:66:66), but it releases around 39.4±0.33% of drug in 2 hrs. Therefore, it was further enteric coated with coating material 5% coded as F1. It prevents the drug release in upper part of GIT and shows 28% of drug release after 2 hrs as compared than other formulations.

CONCLUSION

The aim of this work was to prepare and evaluation colon targeted tablets of Ornidazole using different proportions of shellac, zein and guar gum.

Ornidazole is used for the treatment of several local diseases of colon such as Crohn's disease etc. Formulation containing combination of shellac, zein and guar gum released least amount of drug in the acidic environment of stomach and released most of the drug in colon. It is evident from above discussion that targeted delivery to colon will result in lesser side effects and maximum utilization of drug.

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