WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Formulation and Evaluation of Metronidazole Coated Tablets for Colon Drug Delivery

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ABSTRACT

Amoebiasis (also known as amoebic dysentery) is an infection of large intestine caused by protozoan parasite, Entamoebahistolytica leading to the death of 40–100thousands of people, which makes amoebiasis second only to malaria as a cause of death resulting from protozoan parasite (World Health Organization,1997). The disease can be acute or chronic showing various degree of illness. Thetrophozoites of Entamoebahistolytica can invade the colonic epithelium, causing amoebic colitis. The most preferred choice of drugs for intestinal amoebiasis is Metronidazole.Metronidazole is the preferred drugs used in treatment of the amoebiasis, giradiasis, trichomonasis and anaerobic infections. These drugs are to be delivered tithe colon for their effective action against trophozoites of E. histolytica and Giradia labia wherein the respective trophozoites reside in lumen of the caecum and large intestine and adhere to colonic mucus and epithelial layers. Among all the formulations, However it is seen the F7 formulation is suitable candidate further processing as CTDDS

Key words: Metronidazole Guar gum, Pectin, Carbopol934, Ethylcelluose, Eudragit L100, Eudragit S100 and HPMC K4M.

Introduction

Oral route of drug administration is perhaps the most appealing route for the delivery of drugs.[1-4] Various dosage forms administered orally, the tablets are the most preferred dosage form, because of its ease of An Controlled release drug delivery system can be a major advance towards solving problems concerning the targeting of a drug to a specific organ or tissue and controlling the rate of drug delivery the target site. The development of oral controlled release system has been a challenge to formulation scientist due to their inability to restrain and localize the system at targeted areas of the gastrointestinal tract.Availability of wide variety of polymers and frequent dosing intervals helps the formulation scientist to develop sustained/controlled release products. Oral Controlled release (C.R) products provide an advantage over conventional dosage forms by optimizing bio pharmaceutics pharmacokinetic and pharmacodynamics properties of drugs in such a way that it reduces dosing frequency to an extent that once daily dose is sufficient for therapeutic management through uniform plasma concentration providing maximum utility of drug with reduction in local and systemic side effects and cure or control condition in shortest possibletime by smallest quantity of drug to assure greater patient compliance. Various factorsinfluencing the design and performance of controlled release products along with suitableillustrations.Controlled-release drug systems are more sophisticated than justsimply delaying the release rate and are designed to deliver the drug at specific release rates within apredetermined time period [5-9]. Targeted delivery systems are also considered as a controlled deliverysystem, since they provide spatial control of drug release to a specific site of the body.Advantages of controlled release drug delivery systems include delivery of a drug to the requiredsite, maintenance of drug levels within a desired range, reduced side effects, feweradministrations,and improved patient compliance. However, there are potential disadvantages that should not beoverlooked. Disadvantages of using such delivery systems include possible toxicity of the materialsused, dose dumping, requirement of surgical procedures to implant or remove the system, and highermanufacturing costs. In the pharmaceutical industry, design and development of controlled/sustainedreleasedelivery systems have been used as a strategic means to prolong the proprietary status of drugproducts that are reaching the end of their patent life. A typical example is modifying an existingdrug product that requires several doses a day to a single daily dosing to maintain the dominanceover generic competition. For some drugs, controlled delivery is necessary, since immediate releasedosage forms cannot achieve the desired pharmacological action. These include highly water solubledrugs that need.[10-14]

MATERIALS AND METHODS

Metronidazole were obtained from Torrent Pharmaceuticals Ltd.,Gujrat India. Guar gum, Pectin, Carbopol934, Ethylcelluose, Eudragit L100, Eudragit S100 and HPMC K4M were obtained from Loba chemie Pvt. Ltd., Mumbai.

Direct compression techniques

Direct compression name implies compressing tablets directly from powdered materials without modifying the physical nature of materials itself. Direct compression is generally done by drug directly mixed with excipients. Main advantage of direct compression is it saves time when compared to other methods of compression. Another advantage is in terms of tablet quality i.e. processing without the need of moisture and heat.

Wet granulation technique:

In wet granulation, granules are formed by the addition of a granulation liquid on to a powder.The agitation resulting in the system along with the wetting of the components with the formulation result in aggregation of the primary powder particles to produce wet granules.The granulation liquid contain a solvent which must be volatile so that it can be removed by drying and be non toxic ,Typical liquid include water , ethanol, isopropanol either alone or in

Formula for Metronidazole Compressed coated Tablets.

INGREDIENTS(mg)	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**	**F12**
Metronidazole (core)	200	200	200	200	200	200	200	200	200	200	200	200
Guar gum	200						100					
Pectin		200					100					
Ethyl cellulose			200					100	100	100		
Carbopol 934				200				100				100
HPMC K4M					200				100			
Eudragit S100						200				100	100	100
Eudragit L100											100	
Lactose	35	35	35	35	35	35	35	35	35	35	35	35
Pvp	10	10	10	10	10	10	10	10	10	10	10	10
Mg.stearate	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5

Dissolution Rate Studies

Apparatus : USP Type II (Labindia dissolution apparatus)

Method : Paddle

Dissolution Medium: 0.1N HCL, pH 6.8,pH 7.4 buffer

Volume : 900 ml

Speed : 50 rpm

Temperature :37±0.5°C

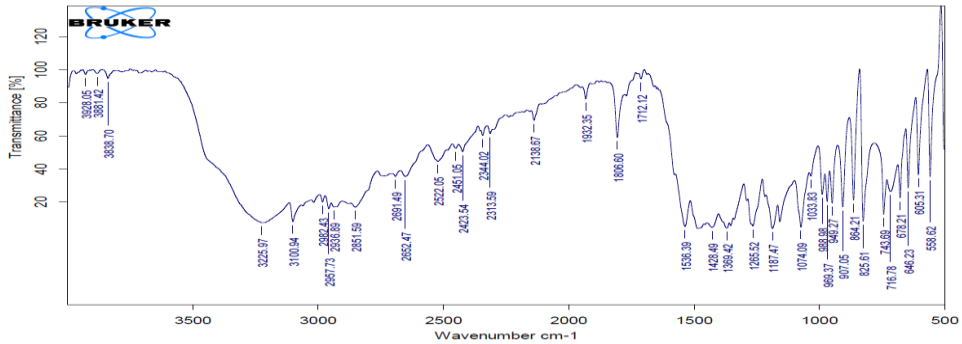
Procedure

Dissolution fluid consisting of 900 ml 0.1N HCL of pH 1.2 ,pH 6.8, pH 7.4 was used in the study. One matrix tablet consists of 160 mg of metronidazole a speed of50 rpm at temperature 37±0.5°C was employed for each test.10 ml samples were withdrawn at different intervals of 30 min ,1hr,2hrs,3hrs,4hrs,5hrs,6hrs,7hrs,8hrs,9hrs,10hrs,11hrs and 12hrs.The volume of dissolution fluid adjusts the 900 ml by replacing 10 ml of dissolution medium after each sampling. Samples withdrawn were assayed at 279 nm for metronidazole. Each drug release experiment was repeated three times (n=3).The results are given in the table (5.10) and as show in figure.

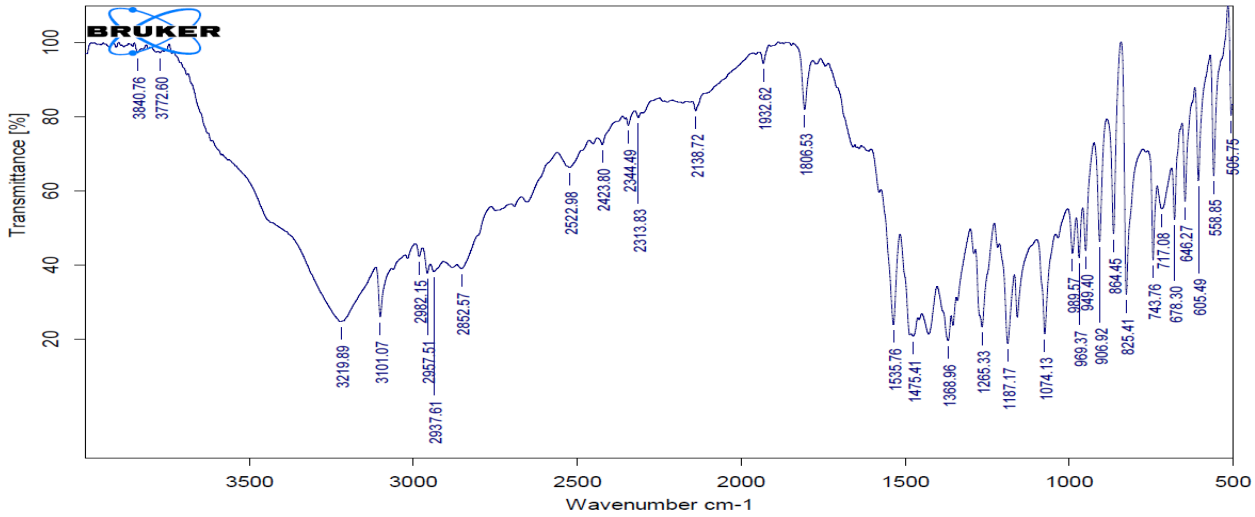
Drug-Polymer Interaction studies:

FT-IR Spectroscopy:

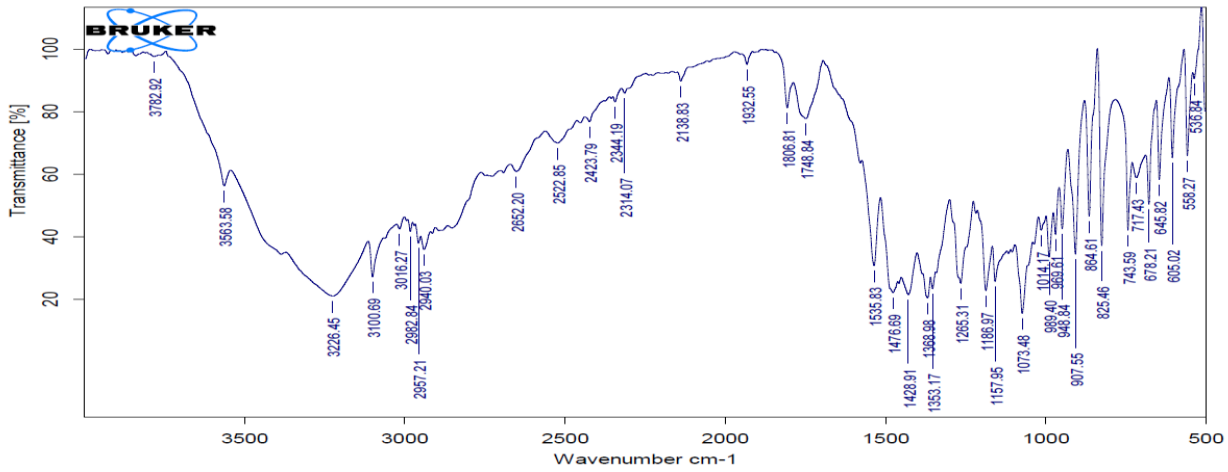
I.R spectra Of Metronidazole:



I.R Spectra of metronidazole and GUARGUM

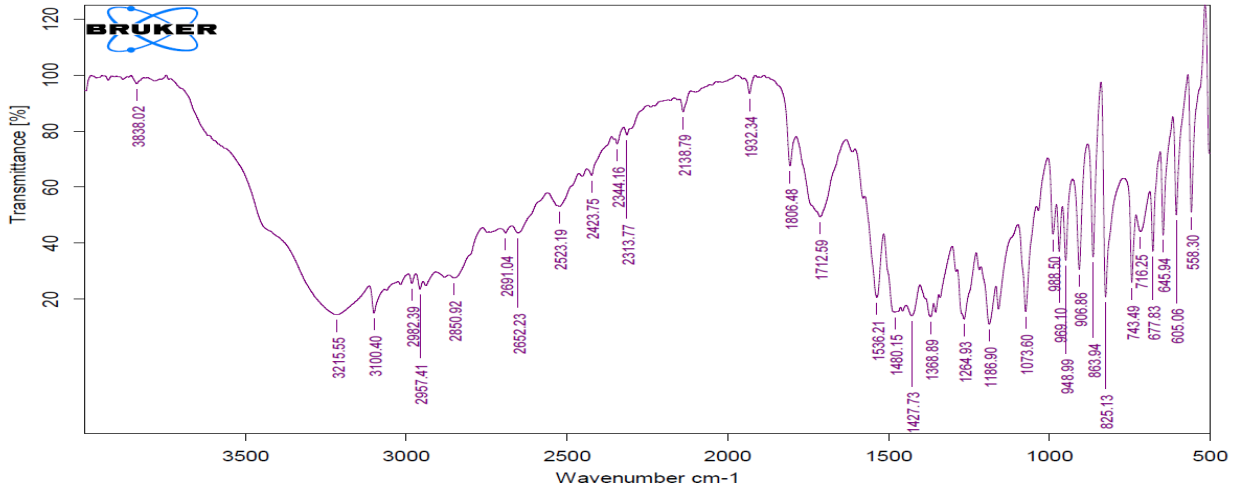


I.R Spectra of metronidazole and PECTIN

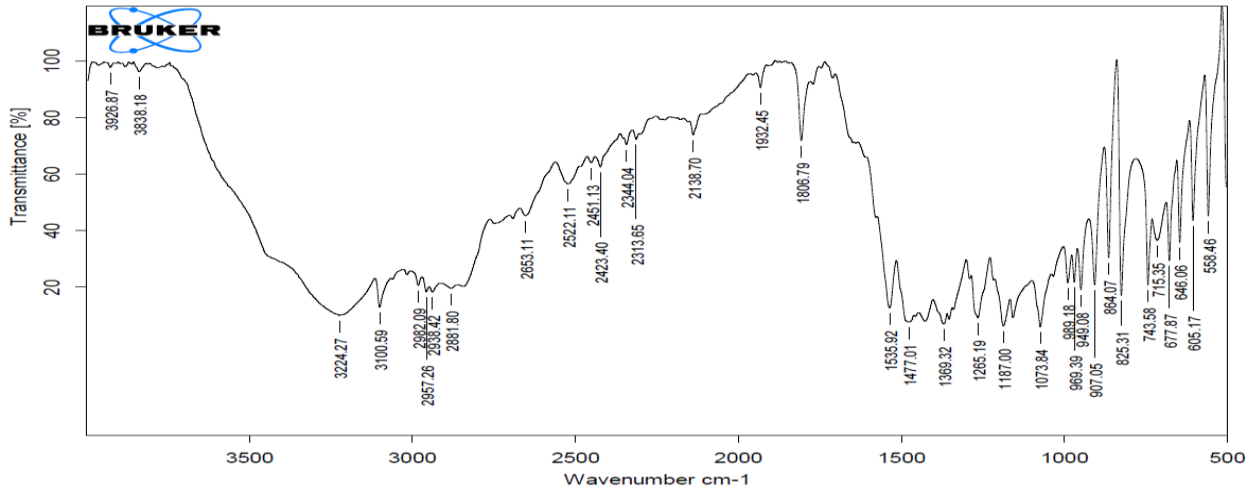


I.R Spectra of metronidazole and ETHYL CELLULOSE

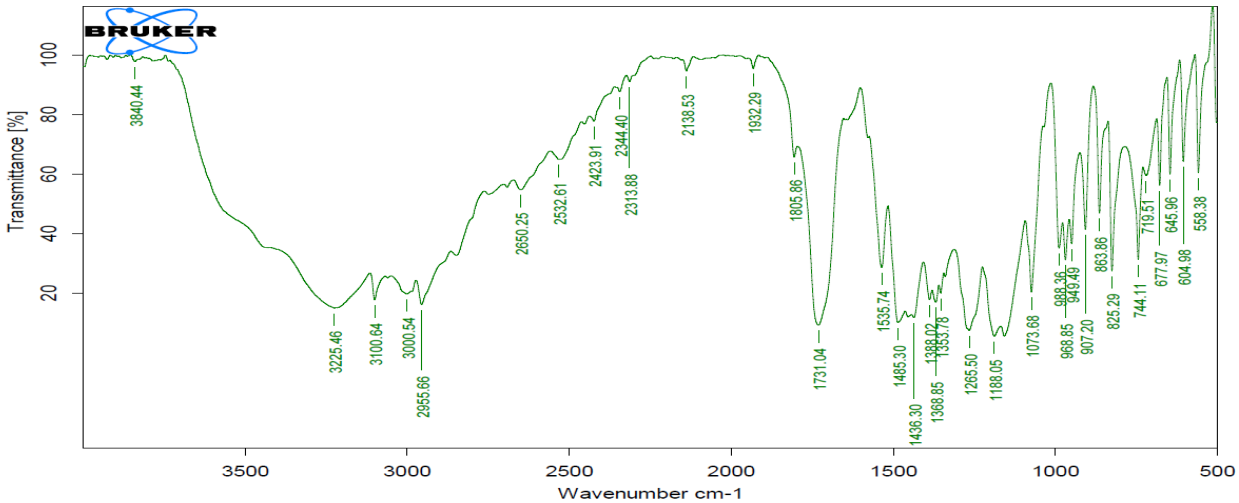
I.R Spectra of metronidazole and CARBOPOL 934



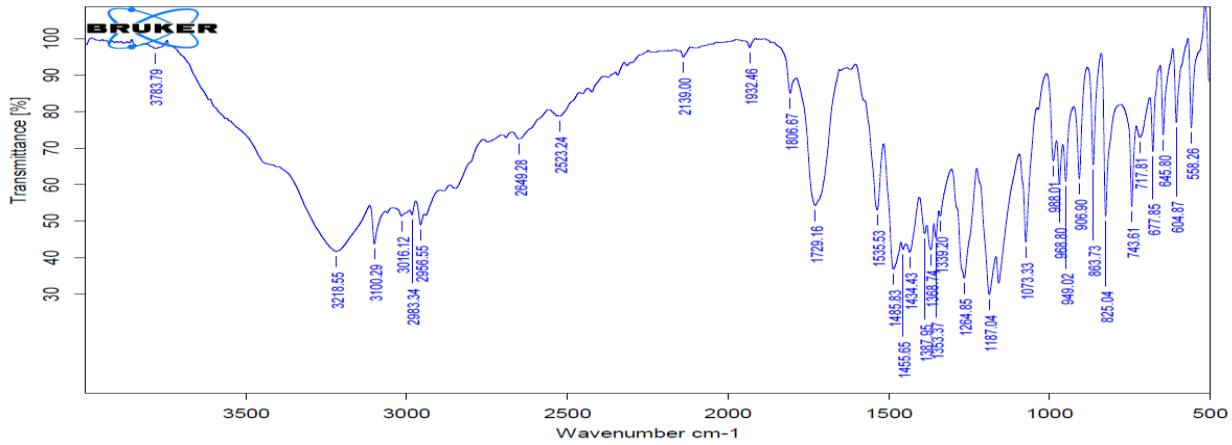
I.R Spectra of metronidazole and HPMC K4M



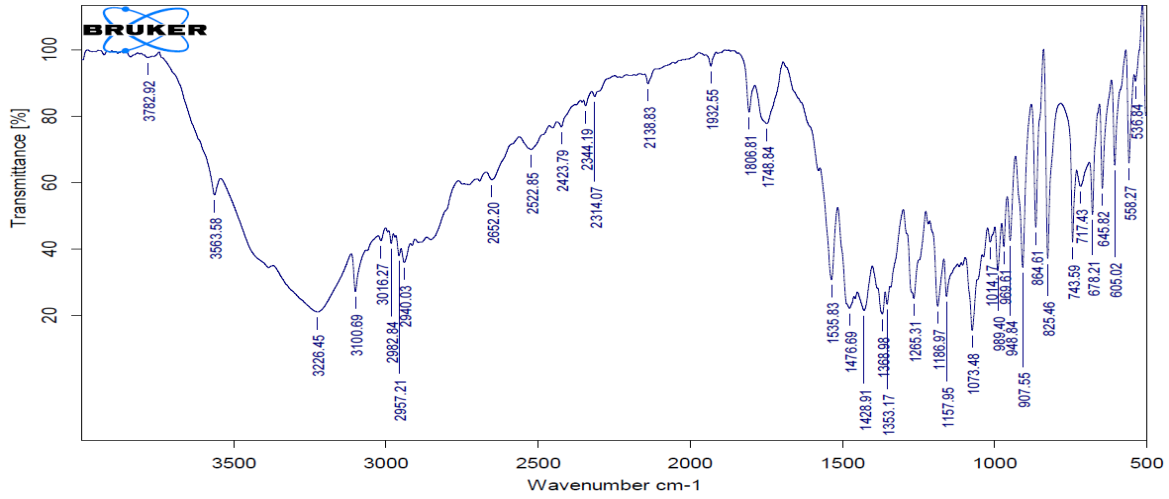
I.R Spectra of metronidazole and EUDRAGIT S100



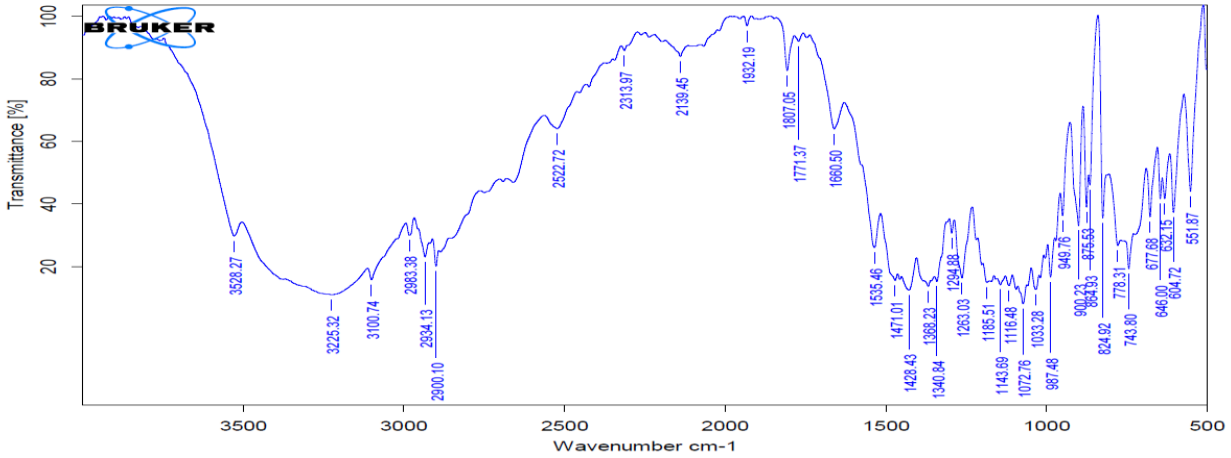
I.R Spectra of metronidazole and EUDRAGIT L100



I.R Spectra of metronidazole and PVP



I.R Spectra of metronidazole and LACTOSE



FTIR interpretation peaks

S.No	IR Spectrum	Peak cm^{-1}	Group	Stretching/ Deformation
1	Metronidazole	3225.95	O-H (alcohol,phenol)	Stretching
		2987.87	=C-H(alkenes)	Stretching
		1536.02	N-O (Nitro)	Stretching
		1074.54	C-N (Aliphatic amines)	Stretching
		678.24	C=H(aromatics)	Stretching
		2522.54	O-H(carboxylic acids)	Stretching
2	Physical mixture of Metronidazole and Guargum	3219.64	O-H (alcohol, phenol)	Stretching
		2987.20	=C-H(alkenes)	Stretching
		1537.61	N-O (Nitro)	Stretching
		1074.96	C-N (Aliphatic amines)	Stretching
		678.58	C=H(aromatics)	Stretching
		2522.55	O-H(carboxylic acids)	Stretching
3	Physical mixture of Metronidazole and Pectin	3226.58	O-H (alcohol, phenol)	Stretching
		2987.42	=C-H(alkenes)	Stretching
		1535.4	N-O (Nitro)	Stretching
		1074.5	C-N (Aliphatic amines)	Stretching
		678.5	C=H(aromatics)	Stretching
		2522.8	O-H(carboxylic acids)	Stretching
4	Physical mixture of Metronidazole and Ethyl cellulose	3225.54	O-H (alcohol, phenol)	Stretching
		2987.5	=C-H(alkenes)	Stretching
		1535.5	N-O (Nitro)	Stretching
		1073.5	C-N (Aliphatic amines)	Stretching
		677.14	C=H(aromatics)	Stretching
		2522.7	O-H(carboxylic acids)	Stretching
5	Physical mixture of Metronidazole and Carbopol 934	3225.8	O-H (alcohol, phenol)	Stretching
		2987.2	=C-H(alkenes)	Stretching
		1536.41	N-O (Nitro)	Stretching
		1074.36	C-N (Aliphatic amines)	Stretching
		678.5	C=H(aromatics)	Stretching
		2523.41	O-H(carboxylic acids)	Stretching
6	Physical mixture of Metronidazole and HPMC K4M	3225.50	O-H (alcohol, phenol)	Stretching
		2987.3	=C-H(alkenes)	Stretching
		1535.48	N-O (Nitro)	Stretching
		1073.2	C-N (Aliphatic amines)	Stretching
		678.2	C=H(aromatics)	Stretching
		2532.9	O-H(carboxylic acids)	Stretching
7	Physical mixture of Metronidazole and Eudragit S100	3225.54	O-H (alcohol, phenol)	Stretching
		2955.5	=C-H(alkenes)	Stretching
		1536.5	N-O (Nitro)	Stretching
		1074.5	C-N (Aliphatic amines)	Stretching
		678.14	C=H(aromatics)	Stretching
		2522.7	O-H(carboxylic acids)	Stretching
8	Physical mixture of Metronidazole and Eudragit L100	3218.8	O-H(carboxylic acids)	Stretching
		2983.2	O-H (alcohol, phenol)	Stretching
		1537.41	=C-H(alkenes)	Stretching
		1073.36	N-O (Nitro)	Stretching
		677.5	C-N (Aliphatic amines)	Stretching
		2523.41	C=H(aromatics)	Stretching
9		3224.50	O-H(carboxylic acids)	Stretching

	Physical mixture of Metronidazole and PVP	2987.3	O-H (alcohol, phenol)	Stretching
		1535.48	=C-H(alkenes)	Stretching
		1074.2	N-O (Nitro)	Stretching
		678.2	C-N (Aliphatic amines)	Stretching
		2522.9	C=H(aromatics)	Stretching
10	Physical mixture of Metronidazole and lactose	3119.50	O-H(carboxylic acids)	Stretching
		2987.3	O-H (alcohol, phenol)	Stretching
		1535.48	=C-H(alkenes)	Stretching
		1074.2	N-O (Nitro)	Stretching
		678.2	C-N (Aliphatic amines)	Stretching
		2522.9	C=H(aromatics)	Stretching

Pre-Compression Parameters of Designed Formulations.

Formulation	Angle of Repose (^{0})	Bulk Density (g/ml)	Tapped Density (g/ml)	Compressibility Index (%)	Hausner Ratio
F1	25.64± 0.01	0.461± 0.08	0.566 ± 003	18.55± 0.09	1.22± 0.02
F2	24.60± 0.02	0.483± 0.01	0.566± 0.09	14.66± 0.02	1.17± 0.01
F3	28.28 ± 0.03	0.484± 0.08	0.517± 0.02	6.382± 0.08	1.06± 0.08
F4	32.33± 0.02	0.365± 0.02	0.389± 0.08	6.16± 0.09	1.06± 0.09
F5	26.56 ± 0.03	0.508± 0.01	0.585 ± 003	13.16± 0.01	1.15 ± 0.03
F6	28.28± 0.08	0.517 ± 0.03	0.612± 0.01	15.52± 0.09	1.18± 0.09
F7	25.64± 0.01	0.483 ± 0.03	0.566± 0.09	14.6± 0.02	1.17± 0.01
F8	29.94 ± 0.03	0.463± 0.09	0.517± 0.02	10.44± 0.02	1.11± 0.09
F9	24.98± 0.08	0.545 ± 0.03	0.652± 0.09	16.41± 0.09	1.202± 0.02
F10	23.17± 0.01	0.491± 0.08	0.566± 0.01	13.25± 0.01	1.152 ± 0.03
F11	25.07 ± 0.03	0.506 ± 0.03	0.632± 0.08	13.19 ± 0.03	1.15± 0.02
F12	25.78 ± 0.01	0.500 ± 0.0	0.545± 0.05	8.25 ± 0.02	1.09± 0.02

Evaluation of compression coating matrix tablets:

Formulation	Weight Variation (%) deviation	Hardness (kg/cm^2)	Friability (%)	% Drug content (%)
F1	-0.22	6.0± 0.03	0.22 ± 0.02	90.92± 0.02
F2	0.44	5.8± 0.04	0.33± 0.02	93.03± 0.02
F3	-0.44	6.3± 0.03	0.	96.56± 0.01
F4	0	6.2± 0.05	0.	92.95± 0.01
F5	0.216	5.7± 0.04	0.33± 0.02	94.29± 0.02
F6	-0.022	5.0± 0.03	0.346± 0.01	96.0± 0.02
F7	0.	6.3± 0.04	0.296 ± 0.02	98.25± 0.01
F8	0.22	5.8± 0.05	0.334± 0.01	96.81± 0.03
F9	0.22	5.5± 0.03	0.	94.75± 0.02
F10	0.66	5.8± 0.05	0.275 ± 0.02	91.7± 0.01
F11	0.66	4.9± 0.04	0.221± 0.01	98.73± 0.03
F12	0	5.48± 0.04	0.22± 0.02	95.0± 0.02

RESULT AND DISCUSSION

- The result of invitro evaluation study done on tablets with formula F1 to F12 and shown in the Tables and Figures.
- A comparative description of different drug release profiles is shown in the table 5.14
- The drug content is uniform in all the batches of tablets produce. The hardness and friability are within Pharmacopeialimits.
- The Disintegration time is gradually increased to max of 3 hrs for F7 formulation which containing the maximum comes of Guargum and Pectin
- Analysis of drug release profile indicates some interesting points ,The formulation F0 (control) tablet release the drug in fastest manner when synthetic andnatural polymers incorporate with causes slower drug release rates increasing concentration of polymers causes fall in drug release rate.

- The Correlation coefficient are very high for both Zero order and First order fit, In all the 12 formulation the Zero order correlation coefficient is higher and hence it was concluded that the drug release rate may be taken to be following a Zero order fit.
- The T_{50} value is for control is found to behrs and gradually rises the peak ofhrs for formulation 7
- The T_{90} value was found to be hrs for controlled F0 formulation and gradually increases peak of hrs in case of for F7.
- The Zero order rate constant K_0 maximum were found to be formulationF4(21.0 hr^{-1}} it get reducing at a formulation of F7(6.93hr^{-1})
- When Peppas equation was used to fit the data obtained in the drug release it was found that the 'n' value ranges from 0.999 to 1.6 this suggested that the drug release Super case II transport.
- A comparative to analysis of the drug release data shown that F7 is totally suitable for use as a colon targeting drug delivery system.
- As it is releasing the drug 35% in first 12 hrs.
- The following are the drug release for remaining polymers for first 12 hrs
- Guargumreleasing the drug 37% in first 12 hrs
- Pectin releasing the drug 67% in first 12 hrs
- Ethyl cellulose releasing the drug 40 % in first 12 hrs
- Carbopol 934 releasing the drug 98% in first 12 hrs
- HPMC K4M releasing the drug 61% in first 12 hrs
- Eudragit S100 releasing the drug 78.6% in first 12 hrs
- Guargum+ pectin releasing the drug 34% in first 12 hrs
- Ethyl cellulose+ Carbopol 934 releasing the drug 94.2% in first 12 hrs
- Ethylcellulose+HPMC K4M releasing the drug 97.4% in first 12 hrs
- Ethyl cellulose + Eudragit S 100 releasing the drug 60.4% in first 12 hrs
- Eudragit S 100 + L100 releasing the drug 70.2% in first 12 hrs
- Carbopol 934 + HPMC K4M releasing the drug 76.6 % in first 12 hrs
- However it is seen the F7 formulation is suitable candidate further processing as CTDDS
- The following was the list of drug release profile various formulation F1 to F12 is given the tablet and shown in figures and it was also observe the individual drug polymers also observed the comparative study of individual polymers with combination.
- The formulations of F1 to F7 are of individual drug and polymers combinations.
- The drug release profile and kinetics shown in figures.
- And the comparison of Drug + two polymers was started from F8 to F12 is shown in figures and tables.
- And from this two methods it was derived that combination of drug with two polymers has shown a good drug release rate. And following is the order of drug release rates.
- F7>F1>F3>F10>F5>F2>F11>F12>F6>F8>F9>F4
- Finally it was concluded that the optimized formula of F7 (Drug + Guargum+Pectin) is shown as a better formulation for producing CTDDS.
- When it is comparative marked product it was found that the optimized formula have shown in better drug release rate and it shown in Table.

CONCLUSION

Metronidazole is the preferred drug used in treatment of the amoebiasis, giradiasis, trichomonasis and anaerobic infections. These drug are to be delivered to the colon for their effective action against trophozoitesof E. histolytica and Giradia lamblia wherein the respective trophozoites reside inlumen of the caecum and large intestine andadhere to colonic mucus and epithelial layers. And it is formulated in the colon targetd drug delivery system by using compression coating technique.

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