PMDJAS E-ISSN: 2789-2611
Pakistan's Multidisciplinary Journal for Arts & Science
ISSN 2789-2611 https://pmdjas.com | May. 2023, VOL. 4 (No, 02) Page. 12 – 22 |

Formulation Development and Characteristics Assessment of Metronidazole Tablets (Colon Specific Coated)

Zartasha Khalid[1], Mahira Tabassum[1], Ghulam Razaque[1], Noman Ul Haq[1], Ghulam Mustafa Shahwani[1], Aqeel Naseem[1], Arshia Sumbal[2]

[1]Faculty of Pharmacy and Health Sciences, University of Balochistan, Quetta.
[2]Department of Zoology, University of Balochistan, Quetta

DOI: https://doi.org/10.5281/zenodo.7903316
Corresponding author: zartasha_khalid@outlook.com

Received April: 06/2023. Accepted May: 01/2023. **Published May: 07/2023.**

Abstract

The system of drug delivery mainly depends on targeted therapy synthesis that is the formulations active pharmaceuticals ingredients from drug will only be released target area, so the action generated by active pharmaceutical ingredients in specific time period depends on formulation of drug therapy. Colon specified drug targeted system either in the form of polymers or in single can be used to obtain the desired and needed therapeutic effect. FTIR were done of active ingredient (Metronidazole and polymers separately and their combination), pre-compression tests (Flowability, Angle of response, compressibility index and Hansner's ratio) were also performed. Solubility studies were also performed with different solvents and temperatures. Two different formulations were prepared F1 and F2 with different drug to polymer ratios were combined by coating two different types of polymers Eudragit and Guar gum. All physical characteristics of both formulations F1 and F2 were performed accordingly and in-vitro dissolution were also done. The results showed that there is no compatibility with drug and polymers. The drug is highly soluble in distilled water. The pre-compression results were within the acceptable range. Both the Formulation F1 and F2 physical characteristics were within the specified limits. The dissolution results of both formulations F1 and F2 showed the absorption of polymer greater from (F1) to (F2) w/w, the drug rate release same comparatively. Comparatively extent of release of drug was observed. It is concluded that this type of research may be conducted for patient bifacial and compliance.

Keywords: Colon Drug Delivery, Metronidazole, Polymer, Eudragit, Guar Gum.

Introduction

The method which directs substance therapeutically through common administration routes so that adequate or definite therapeutic outcome is achieved both in animals and humans. In this ground the main facts are increasing the drug safety, efficacy and effectiveness. The system of drug delivery mainly depends on targeted therapy synthesis that is the

formulations active pharmaceuticals ingredients from drug will only be released target area, so the action generated by active pharmaceutical ingredients in specific time period depends on formulation of drug therapy. That is why the therapy designed must be in pattern that it should the deliver results desired in specific site of action and not to interact with human immune system (Hassan, December 10, 2012).

Targeted delivery of drugs also called as smart delivery of drug is basically a framework of drugs administered that comprises of medication flow to show the desired actions in body compartments either in one or few when compared with others medications (Mishra et al., 2016). So, it distributes the medications in areas designed specifically for which ultimately provides improvement if effectiveness of therapy for treatments and reduces the ADRs related to medications (Rani & Paliwal, 2014).

Effective delivery of a pharmaceutical Medicine applied to the colon it requires the drug which protected from the gastrointestinal tract (GIT) enzymes, barriers that release the drug in to the stomach or it is said to be degradation or and then CR of drug or drug contents in colon (Vyas & Khar, 2002).

Colon specified drug targeted system either in the form of polymers or in single can be used to obtain the desired and needed therapeutic effect. Because it is now documented that polymers can have great release drug effect, absorption and distribution of medicine shows vital roles in Colon specified drug targeted system formulation (Rajpurohit, Sharma, Sharma, & Bhandari, 2010).

Colon specified drug targeted system is a comparatively new application for the diseases of ulcerative colitis also in the treatment of the Irritable bowel syndrome and most specifically in the treatment of the Crohn's disease. Polymers that are pH-sensitive utilized that soluble the active ingredient and applied for the action in colonic region (Sonje & Chandra, 2013).

Polymers are made by number of subunits having large molecular weight which consist of different functional group, which can be mixed with one another entities and substances (Swati, Achhrish, & Sandeep, 2012).

Use of polymers while manufacturing novel system of drug delivery are gaining importance and due to the advancement in science of polymer in drug delivery system there is better development and technology of polymer use in novel drug delivery (Raizada).

These advance and new development in technology mainly emphasize on delivering drugs which is career bases and to in improving drugs by chemicals and also in matrices that are polymers that are drug entrapment and placing in different pumps modified which are injected or inserted in body compartment required. These ultimate new technical advancement and approaches by which drug is delivered to desired area lead to comparatively better use medications that ultimately made human practicing better and improved and a lot of researches are directed or attracted towards polymeric material use while manufacturing novel drugs (Godwin et al., 2001).

Objectives and aim of the current study were to formulation of colon specific drug delivery system of metronidazole compressed tablets with different ratios of Eudragit RL100, pectin, guar gum were used. To release the drug at pH of colonic fluid Eudragit RL100 coating will be used for compression coating tablets. Compression coated tablets released drug in a combine mechanism specifies biodegradability of polymers and pH dependent.

Research methodology:

All the equipment's, glassware and chemicals used in this research were received from different venders and few were received as gift for this research work, metronidazole received as a gift sample from Lahore.

Eudragit RL100 (China) purchased, pactum, guar gum (China) purchased, lactose available in the lab of faculty of Pharmacy University of Balochistan, Quetta, starch, magnesium stearate both were purchased from Lahore, trisodium, talc, acetone from the Lab, hydrochloric acid from Lahore, sodium hydroxide, all the chemicals were used in this research.

Drug Polymer Compatibility Studies:

FTIR (Fourier Transform Infrared Radiation): for the best design and formulation of dosage form physical, chemical, and biological qualities of the drug and excipients of the drug used in the manufacturing products. In order to create a product that is stable, effective, appealing, and safe compatibility between the active ingredient and other excipients must be established. Hence, earlier to create the formulation, metronidazole compatibility with other different polymers different excipients were tested by using FT-IR spectroscopy. Scanned samples were over the wave number region 4000-400 cm^{-1}. Small amount of the mixture was spread uniformly over zinc selanide lens and then pressure was applied and then after scanned in the IR region. The result of IR spectra of samples were matched with the standard IR spectra(Mehta, Chawla et al. 2013).

Pre-formulation Studies: Pre-formulation studies formulation development of this will be carried out which helps formulation development if found any problem before formulation development it will be addressed and the problem will be removed if any (Khirwadkar & Dashora, 2003).

The following Pre-formulation studies will be carried out in the studies to check the physical and chemical description of all the substances. (Khirwadkar & Dashora, 2003).

Standard curve.

The standard curve of metronidazole were performed and prepared stock solution (250micro gram/ml) by dissolving 100 mg of active ingredient (metronidazole) in the 0.1M HCL solvent, 96% ethanol and these solutions were diluted to 200 ml. five different dilutions were made1mg/ml 0.5mg/ml, 0.025mg/ml, 0.0125mg/ml and 0.00625mg/ml of metronidazole and analyzed with the help of UV-Visible spectroscopy at 240 nm.

Solubility: 100mg drug of each drug (metronidazole) was incorporated with 100ml volumetric flask with different solvent (distilled water, phosphate buffers pH 6.8 and 7.4) at 25c, 37 c and 40c for 24 hours in shaker water bath. The flask was covered with aluminum foils. Samples of 10 ml were taken and passed through membrane filter (0.45µ). Absorbance were noted at spectrophotometrically by using the apparatus UV- visible spectrophotometer at a wavelength of 240 nm for metronidazole.

Table of drug solubility of metronidazole

Drug	**Solvent**	**Temperature**
Metronidazole	Distilled water	25c
Metronidazole	Distilled water	37c
Metronidazole	Distilled water	40c
Drug	Solvent	Temperature
Metronidazole	PH buffer 6.8	25c
Metronidazole	pH buffer 6.8	37c
Metronidazole	pH buffer 6.8	40c
Drug	Solvent	Temperature
Metronidazole	PH buffer 7.4	25c
Metronidazole	pH buffer 7.4	37c
Metronidazole	pH buffer 7.4	40c

Tap density: The powder sample was mechanically tapped to achieve the increased bulk density known as the tapped density. By mechanically tapping a graduated measuring cylinder or vessel containing the powder sample, the tapped density is produced. The measuring cylinder or vessel is mechanically tapped after the initial powder volume or mass is observed, and volume or mass reading are taken until little further volume or mass change is observed. Raising the cylinder and allow it to drop mechanical tapping is achieved within its own mass. The mechanical tapping is achieved by raising the cylinder or vessel and allowing it to drop, under its own mass. To reduce the possibility of the mass separating during tapping down, devices that rotate the cylinder or vessel may be used.

$$\text{Tapped density} = \frac{\text{weight of powder}}{\text{Tapped volume}}$$

Flow ability: It is a specific characteristic of the bulk powder. The term "Flow able" refers to powder that can flow when it undergoes an irreversible deformation as a result of an external force. Various parameters such Carr's index, flow function, Hausner's ratio, angle of repose as are used to express flowability of powders.

Compressibility index (Carr's index): The cars index was developed to measuring the powder flow form bulk densities. The strength and stability of a powder arch can be directly determined by the percentage of compressibility of the powder. It is calculated according to the following equation,

Carr's index % = tapped density- bulk density / tapped density ×100

Hausner's ratio: Hausner's ratio is an indirect index of ease of powder flow. If the hausner's ratio of powder is near to 1.25indicate better powder flow. It is calculated by the following formula,

$$\text{Hausner's ratio} = \frac{\text{Tapped density of powder}}{\text{Bulk density of powder}}$$

Angle of repose: It describes the largest angle that may be formed between the surface of the powder quantity and horizontal plane. The powder's angle of repose was obtained using the fixed funnel method. Evaluate the flow property of the granules powder, funnel height was set in such a manner in which the tip of the funnel touches the powder layers above a paper which was placed horizontal flat plane. Weighed powder was taken in the beaker. Cone shaped surface of paper allow to flow the freely by using funnel. Height and diameter of the pile was noted. Radius was calculated from the diameter. The results were tabulated.

Formulation Development of Metronidazole Compression Coated Tablets:

Direct compression method was use to prepare the 2 batch of tablets which contains 50mg metronidazole and weigh about 200mg pectin matrices, guar gum and Eudragit RL100 coating is used as excipient. Metronidazole polymer pectin, mcc and guar gum were well triturated and passed through sieve # no30. The mortar was used to mix the powder separately. Starch was used in hot condition as a binder in the ratio of 10% w/v. After addition of magnesium stearate and talc granules were prepared by using wet granulation method. Bulk density, flow property and compressibility were evaluated through granules. Punch machine was used to punch the tablets from granules to get 200mg tablets of average weight (M. Praveen Kumar et al., 2011).

The powder mas will be poured into hoppers of the apparatus and punched, 200mg average weight will be obtained. Eudragit RL100 will be taken separately for preparation of multi layered tablets of average weight of 200 mg by using punch machine (M. Praveen Kumar et al., 2011).

Formulation Development of Metronidazole Compression Coated Tablets:

Formulation	Ratio	Drug	Polymers	Lactose	Starch	Megnasium
F1	1:1	50mg	50	86.50	12.5	1mg

F2	1:1.5	50mg	75	62.5	12.5	1mg

Evaluation of Drug: Evaluation of the tablet after formulation through different official and unofficial quality control tests like diameter and thickness of the tablets, hardness test, weight variation test, friability test, drug content uniformity and vitro dissolution test.

Diameter and Thickness: Using Vernier calipers to measure the diameter and thickness of the tablets. The standard value of the thickness is ± 5 that is depending on the size of the tablet. The result listed in table(Kumar, Ishaq et al. 2011).

Uniformity of weight: Individually and collectively weight the 20 tablets, average weight determined that the tablets were within the limits. The tablets were compares with IP test if more than two tablets are not in the limit. 20 tablets were weighed collectively and individually from the collective weight, average weight was to ascertain whether it is within permissible limits or not. if no tablets differ by more than 2 times the percentage limit. The result listed in table(Kumar, Prathibha et al. 2012).

Hardness: Monsanto tester was used to measure the hardness of the tablet. Between two plungers having a spring which is compressible. Tablet was placed at lower plunger and reading was zero. Applying a force until tablet was fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The result listed in table(Alkazzaz and Ali 2015).

Friability: Two compartments divided in circular plastic chamber. The apparatus was used name rocher friabilitor. Rotate the tablets at the speed of 20 rpm and dropped the tablets by 15cm distance. In the apparatus pre weighed tablets were placed and given 100rpm and once again weigh the tablets. Difference between two weights represents the friability of the tablet which should not be accessed 1%. Result shown in table(Sharma, Joshi et al. 2012).

Drug content: Formulation 20 tablets were weighed and powdered. The quantity of powder is equal to 50mg of metronidazole drug and this powder is transferred into 100 ml with 0.1N hydrochloric acid for 2 hours. Suitable dilution was filtered and absorbance was measured by UV- spectrophotometer at 276nm.The result shown in table(Sharma, Joshi et al. 2012).

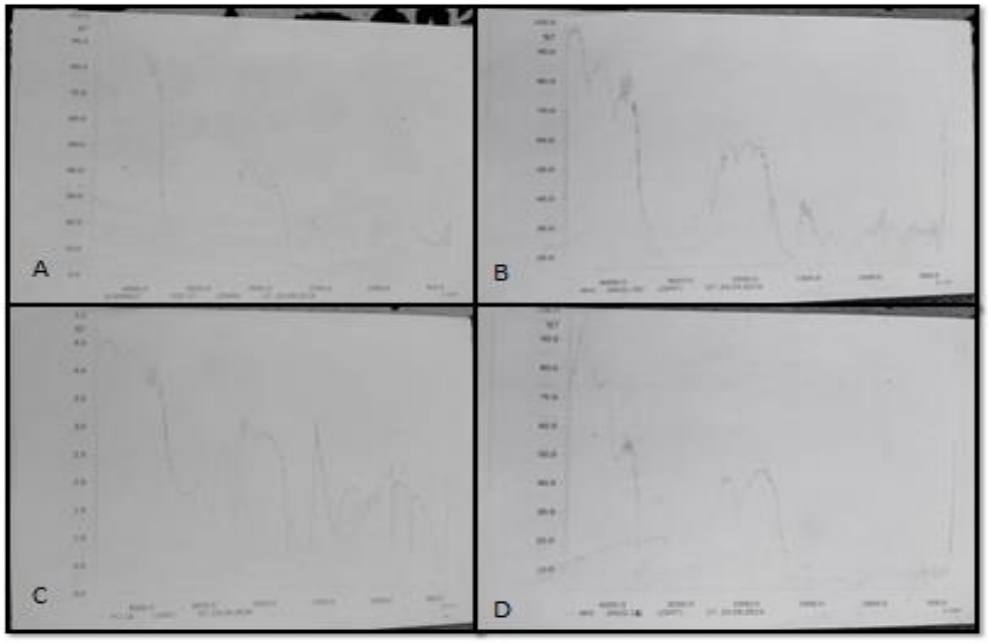
Dissolution study: this study was done by taking both formulations separately one by one and placed in dissolution apparatus USP standard peddle method. According to the standard procedures all the assemblies were filled with 0.1 N 900 ml. the temperature was kept 37± 5 constant for 12 hours at the rate of 100 rounds per minute and readings were collected in different time intervals i.e. 1 hour, 3-hour, 6-hour, 8 hour and 12 hours. After that the samples were analyzed spectrophotometrically with the help of UV-Visible spectrophotometer at 276nm (Mehta, Chawla et al. 2013)

RESULTS AND DISCUSSION:

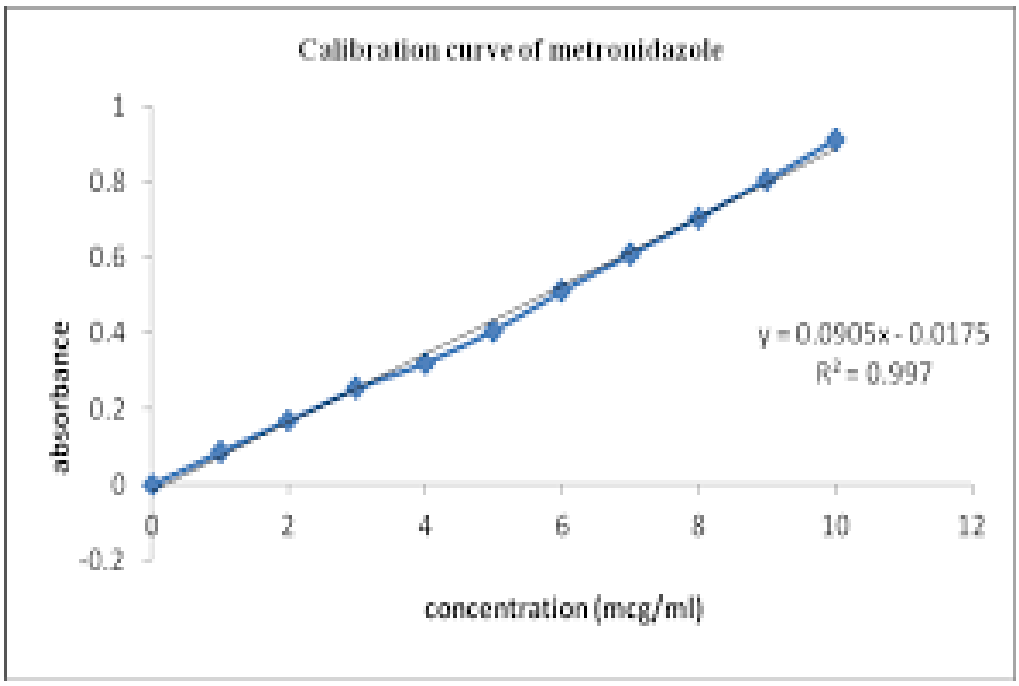
FTIR:

As per I.P the FT-IR used to perform the metronidazole identification. With ratio 1:1 polymers (Eudragit, Guar gum and Pectin) was mixed with metronidazole. For storage the temperature was 25c, 37c, 40c. Study the interaction between polymer and metronidazole.

Peak of the analysis represented that no interaction found between the polymer and drug, also no change in color was observed. The result showed that metronidazole is compatible with polymers. FT-I



R results shown in figure 1. Figure. 1 FT-IR results (A) Metronidazole with Eudragit-RL100 (B) Metronidazole with Guar gum (C) Metronidazole with pectin (D) Metronidazole with polymer



Graph 1. Standard Curve /Calibration Curve of Metronidazole

Table 2. Solubility of the metronidazole

Drug	Solvent	Temperature	Solubility
Metronidazole	Distilled water	25c	7.81±0.03
Metronidazole	Distilled water	37c	7.95±0.02
Metronidazole	Distilled water	40c	7.56±0.03
Metronidazole	PH buffer 6.8	25c	6.91±0.02
Metronidazole	pH buffer 6.8	37c	6.92±0.03
Metronidazole	pH buffer 6.8	40c	6.92±0.02
Metronidazole	PH buffer 7.4	25c	5.81±0.01
Metronidazole	pH buffer 7.4	37c	5.74±0.02
Metronidazole	pH buffer 7.4	40c	5.92±0.03

The solubility of the metronidazole was done in three different solvents (distilled water, pH buffer 6.8 and 7.4, the results were showed in above table that the solubility of metronidazole was good in distilled water comparatively.

Table 3. Pre-compression tests

Formulation	**Angle of repose(*')**	**Bulk density**	**Carr's index**
F1	$25^0$36'	0.467	10.72
F2	$24^0$56'	0.478	11.75

Both formulations show the bulk density was in ranged between 0.467-0.478. the angle of repose for both batches ranged between 24^o36'-$24^0$56'. Good flow property was shown in all formulations, angle of repose value was (25^0 -30^o). Bulk density shows good packaging characters. Free flowing materials was indicated by carr's index value

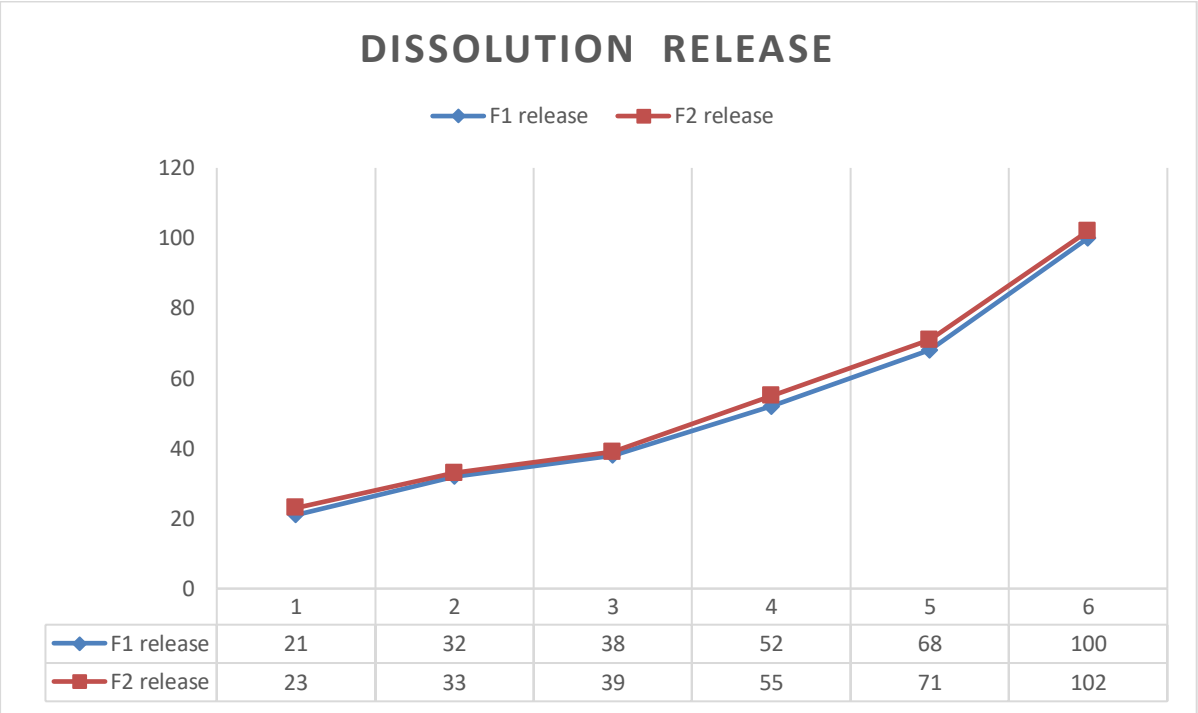
Table 4. Evaluation of Metronidazole

Formulation	Thickness mm	Diameter mm	Percentage friability(%)	Hardness (kg/cm^2)	Weight Variation (gm)
F1	3.5±0.01	8.1±0.02	0.46	4.89±0.02	3.89±0.01

F2	3.6±0.02	8.2±0.11	0.51	5.32±0.31	3.81±0.02

Evaluation of the prepared tablets were undergoing in weight-variation, friability, hardness, drug content test, and dissolution test.

In the range of 3.5-3.6mm of tablet the thickness was shown in table. The I.P specification was observed in weight variation test and the value is shown in table. In range of 4.89±0.02-5.32±0.31 kg/cm^2 the hardness was observed. Both formulations the friability was study in the range of 0.46-0.51. Above parameters shows the result in the recommended ranges. Hardness and friability test show good handling property of the metronidazole tablets.



Graph: 2 Dissolution Test of Metronidazole

The dissolution profiles of pH6.8(7h). Dissolution apparatus (USP XXII apparatus-2) were used to determined dissolution through buffer solutions of 0.1N hydrochloric acid, pH 7.4 for both formulations.

The effect of both the polymers Eudragit RL100 and Guar gum and pectin absorption of the drug release of metronidazole tablets. As the absorption of polymer better from (F1) to (F2) w/w, the released of drug rate same comparatively. Also a comparative release of drug is less was observed. The drug released depend on the nature of matrix but also depend on the polymers ratio. The solubility of Eudragit is totally pH independent. Both the polymers (Eudragit RL100 and Guar gum), which formed a strong bond when contacted with the aqueous media this is very useful in controlled delivery that is especially for the highly water soluble drug. According to the current studies the metronidazole sustained release

formulation releases a drug should be of 21.2% in 1 h, 32.20 in 3 h, 38.8% in 4 h, 52.3 in 6 h, 68.2% in 8 h and 100.4% in 12 h in F1 and 23.3% in 1 h, 33.10 in 3 h, 39.7% in 4 h, 55.2 in 6 h, 71.5% in 8 h and 102.1% in 12 h in F2. Conversely, small intestine and stomach physiological environment release premature drug from cores of the tablet and multilayer tablets that is unable to protect the tablet release from drug.

CONCLUSION:

The colon drug delivery of metronidazole tablet was prepare with different polymer combinations. All the Pre-formulation studies and post compression studies were done and it was concluded that Both the Formulation F1 and F2 physical characteristics were within the specified limits. The dissolution results of both formulations F1 and F2 showed the absorption of polymer greater from (F1) to (F2) w/w, the release drug rate same relatively. Also, a comparative decline in the release of drug was observed. It is concluded that this type of research may be conducted for patient bifacial and compliance.

REFERENCES

Alkazzaz, S. Z. M. and W. K. Ali (2015). "Design and in-vitro evaluation of colon targeted prednisolone solid dispersion tablets." *Pharmaceutical and Biosciences Journal: 30-41*.

Godwin, A., Bolina, K., Clochard, M., Dinand, E., Rankin, S., Simic, S., & Brocchini, S. (2001). New strategies for polymer development in pharmaceutical science—a short review. *Journal of Pharmacy and Pharmacology*, *53*(9), 1175-1184.

Hassan, B. A. R. (December 10, 2012). Overview on Drug Delivery System. *Pharmaceut Anal Acta*.

Kumar, M. P., et al. (2011). "Formulation and evaluation of colon specific matrix and coated tablet of metronidazole." *Int Res J Pharm* ***2****(9): 194-199.*

Kumar, S. P., et al. (2012). "Novel colon specific drug delivery system: A Review." *Int J Pharm Pharm Sci* ***4****(Suppl 1): 22-29.*

Mehta, R., et al. (2013). "Formulation and in vitro evaluation of Eudragit S-100 coated *pharmaceutical technology & research* ***4****(1): 31.*

naproxen matrix tablets for colon-targeted drug delivery system." *Journal of advanced* Khirwadkar, P., & Dashora, K. (2003). Formulation and evaluation of fast dissolving tablets Atenolol. *Journal of Chemical and Pharmaceutical Research*, *6*(2), 113-119.

Patel, M. M. and A. F. Amin (2011). "Formulation and development of release modulated colon targeted system of meloxicam for potential application in the prophylaxis of colorectal cancer." *Drug delivery* ***18****(4): 281-293.*

Patel, R., et al. (2010). "Design Optimization and Evaluation of pH Responsive Prednisolone Sustained Release Tablet for Ileo-colonic Delivery."

Raizada, A. Polymers in drug delivery: a review.

Rajpurohit, H., Sharma, P., Sharma, S., & Bhandari, A. (2010). *Polymers for Colon Targeted Drug Delivery* (Vol. 72).

Rani, K., & Paliwal, S. (2014). A review on targeted drug delivery: Its entire focus on advanced therapeutics and diagnostics. *Sch. J. App. Med. Sci*, *2*(1C), 328-331.

Sharma, M., et al. (2012). "Formulation and evaluation of colon targeted tablets of mesalazine." *Journal of Drug Delivery and Therapeutics* ***2****(5).*

Singh, S. and A. K. Mahato (2016). "Formulation and evaluation of metronidazole tableted microspheres for colon drug delivery." *Asian Journal of Pharmaceutical and Clinical Research: 398-403.*

Sonje, A., & Chandra, A. (2013). Comprehensive review on Eudragit polymers. *Int Res J Pharm*, *4*(5), 71-74.

Swati, A., Achhrish, G., & Sandeep, S. (2012). Drug delivery: special emphasis given on biodegradable polymers. *Adv Polym Sci Technol*, *2*, 1-15.

Vyas, S., & Khar, R. (2002). Systems for colon specific delivery. *Controlled drug delivery: Concept and advantages. 1st ed. Delhi: Vallabh Prakashan*, 218-256.