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# FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY SYSTEM OF METRONIDAZOLE USING COATED MINI TABLETS APPROACH

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## ABSTRACT

The present work is mainly concentrated on designing oral tablet dosage forms of Metronidazole tablets for the treatment of the colonic inflammatory diseases. In the present work of investigation an attempt has been made to design tablet dosage formulations for colon inflammatory diseases. pH sensitive drug delivery has been chosen for the delivery of drug in the colon. The pH sensitive polymers like Eudragit S-100 and Eudragit L-100 are disintegrated at their threshold pH i.e., at pH 7 & pH 6. From the results it was concluded that TF 5 containing core tablet composition was optimized. TF5 tablets were used for the coating of all (EC1 to ECL15) coating solutions. The tablets coated with ethyl cellulose failed to retain the coating at 3 hour of media change (pH 6.8). The coat was floated on the media without disintegration. It was not sticking to the core tablet due to hydration. The tablets coated with ES11, EL13, ECS14 coating solutions were optimized. They showed the lag time of 5 hours and drug was released less than 10% at 5 hour. The single unit tablets showed better results over multiple unit tablets. This is because the multiple unit tablets got less percentage of coating than the single units. The multiple units were coated in conventional coating pan along with the single unit tablets at 15 psi of atomizing air pressure. The EC1 to EC8 coated tablets were failed to retain the coating. Hence the attempts were made to improve the EC coating with combination of ES-100 and EL-100. The tablets coated with ECS14 coating solution shows 5 hour lag time out of all EC containing formulations. This is because of 15 %TWG of EC coating (primary

coating) and 5 % TWG of ES-100 (secondary coating). The outer most ES-100 layer protects the formulation from earlier peel off problem in 6.8 pH phosphate buffer.

**KEYWORDS:** Eudragit S-100 and Eudragit L-100.

## INTRODUCTION

Pharmaceutical industry has always maintained and enjoyed strong financial earnings and business growth. Such healthy growth is not only made possible by launching new products but also by life cycle management of older, existing products, which is playing an increasingly significant role. This aspect becomes even more important once the revenue drops significantly from the existing molecule due to patent protection expiry. Controlled rate, slow delivery and targeted delivery are some of the focus systems that are being pursued vigorously in light of patients' needs and also to succeed in today's competitive business world.

The present work is mainly concentrated on designing oral tablet dosage forms for the treatment of the diseases pertaining to inflammation of colon. The management of the colonic inflammatory disease is poor as drug is largely absorbed in the upper GIT region, before reaching to the colon, in the present work of investigation efforts have been made to design tablet dosage formulations for colon inflammatory diseases. pH sensitive drug delivery has been chosen for the delivery of drug to colon. The pH sensitive polymers likeEudragit L-100 and Eudragit S-100are disintegrated at their threshold pH i.e., at pH 7 & pH 6. These polymers deliver the drug at colonic pH. By this, the desired concentrations of drug in the colon will be maintained throughout the treatment.

### Drug Profile

**Metronidazole:** It's a 5-nitroimidazole derivative routinely prescribed to treat amoebiasis, trichomoniasis infections, vaginitis, anaerobic bacteria, giardiasis, and treponemal infections. It has also been in question as a radiation sensitizer for hypoxic.

**Mechanism of Action:** Metronidazole is antiprotozoal, bactericidal, and trichomoncidal. The exact mechanism of action has not been fully explicated. The mechanism of action appears to be that the Unionized Metronidazole is reduced by low-redox-potential electron transfer enzymes, nitroreductases to unidentified polar products which lack the nitro group. The reduction products seems to be responsible for the cytotoxic and antimicrobial effects of the

drug by covalently binds to DNA, causing disruption of its helical structure, inhibiting bacterial nucleic acid synthesis and resulting in bacterial cell death.

**Preformulation Study**

**FT-IR Spectroscopy:** In the present study, the compatibility between the drug Metronidazole with different polymers and excipients such as Eudragit L 100, Eudragit S 100, HPMC K4M, microcrystalline cellulose (Avicel PH101) were evaluated with help of FT-IR (PERKIN ELMER FT-I Insf. USA). Different physical mixtures of Metronidazole and the polymers or excipients (1:1) were separately mixed with 3 parts of potassium bromide and they were compressed to form pellets in a hydraulic press at 10 tones of pressure. The samples were scanned from 4000 to 400 cm $^{-1}$in FT-IR spectrophotometer. Similarly the IR spectra of all the individual drug and the polymers or excipients were also recorded. Physical appearance of the samples and appearance or disappearances of peaks in the spectra were observed to access any possible physical and chemical interaction.

**METHODS**

**Preparation of Metronidazole tablets and Mini tablets**

**Wet granulation:** Metronidazole granules for tableting were made by wet granulation method. Definite quantities of Metronidazole, HPMC K4M, Avicel PH 101 were weighed and transferred into a mortar according to the formula in table. 9. A wet mass of the mixture passed through a sieve no 18 and tray dried at 40$^{o}$C for half an hour. Different fractions of granules were collected, screened and stored for further studies. Talc and Magnesium stearate were added and mixed for compression of tablets.

**Preparation of Metronidazole tablets:** The Metronidazole compressed tablets were made by manual wet granulation method. The Metronidazole, different proportions of HPMC K4M and Avicel PH 101 (MCC) as main filler and water as granulating fluid, mixed well to obtain a sluggy mass. This mass was passed through sieve no. 18 and dried in a tray drier at 40$^{o}$C for 30 minutes. After drying the granules was again passed into sieve no. 18, the fine, almost uniform granules was obtained. Other manufacturing excipients such as talc 2% and magnesium stearate 1% were also added and thoroughly mixed. An ideal mixture was directly punched in to tablets weighing about 615 mg containing 500 mg of Metronidazole, which were compressed in Rotary tablet punching machine, 16 station (Riddhi) using 13.5 mm * 8 mm capsule shaped concave punches. Prepared Metronidazole compressed tablets of different batches were collected and stored in air tight containers.

**Table. Formula for the preparation of Metronidazole tablets.**

| Ingredients | Percentage w/w | | | | |
|---|---|---|---|---|---|
| | TF1 | TF2 | TF3 | TF4 | TF5 |
| Metronidazole | 500 | 500 | 500 | 500 | 500 |
| HPMC K4M | - | 15 | 20 | 25 | 35 |
| Avicel PH 101 | 100 | 85 | 80 | 75 | 65 |
| Talc | 10 | 10 | 10 | 10 | 10 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 |
| Water | q.s | q.s | q.s | q.s | q.s |

**Preparation of Metronidazole mini tablets (multiple units)**

The Metronidazole mini tablets were prepared by same method described above. 31 mg of Metronidazole granules were weighed and punched into tablets by using 3.0 mm concave punches. The Mini tablets weighing 620 mg (extra 5 mg of MCC was added to the earlier formula) i.e., 31 mg * 20 tablets were calculated and coated with pH sensitive polymers, then they are filled into hard gelatin capsules of size 0.

**Preparation of coating solution**

**Eudragit S-100 solution:** Coating solution was prepared by dissolving 6 gm of Eudragit S-100, dibutyl phthalate (33.3%) as plasticizer, 2% (to the weight of polymer) of $TiO_2$ as opacifying agent in isopropyl alcohol. $TiO_2$wasadded to isopropyl alcohol and filtered. This is added to the polymer solution. Dibutyl phthalate was added volume made to prescribed quantity with remaining solvent mixture with continuous stirring on magnetic stirrer for 1 hr followed by filtration.

**Table. Composition of Eudragit S-100 coating solution.**

| Ingredients | Quantity |
|---|---|
| Eudragit S-100 | 6.0gm |
| Titanium dioxide | 2% (of the weight of polymer) |
| Dibutyl phthalate | 33.3% (of the weight of polymer) |
| Isopropyl alcohol | 100 ml |
| Sunset yellow | 2 mg |

**Eudragit L-100 solution**

The method used was same as mentioned in Eudragit S-100 coating solution.

**Ethyl cellulose solution**

The ethyl cellulose coating solution was made by solubilizing 15% of ethyl cellulose as an enteric polymer, dibutyl phthalate and isopropyl alcohol was used as solvent. The method was same as mentioned in Eudragit S-100 solution.

**Coating of Metronidazole tablets**

About 100 gm (50 numbers of Metronidazole tablets and rest of them are dummy tablets which was round in shape) of compressed Metronidazole tablets were de-dusted and loaded in a 8 cm width mini stainless steel coating pan which was fixed on VJ instruments laboratory coating machine, 25 rpm was maintained. The tablets loaded bed was pre-heated at 60°C. The prepared Eudragit S-100 (6%w/w)coating solution was sprayed on the tablet bed, spay gun nozzle 0.52 mm diameter, air pressure at 1 bar (10 psi), spray rate 2 ml/ min and the hot air was applied inside coating pan at 50-60°c. The coating process was continued until the desired tablet coating weight was achieved. The final tablets were kept in aluminium foil to prevent coating damage and standard evaluations like weight variation, uniformity of drug content and *in-vitro* dissolution study were conducted.

**Coating of Metronidazole Mini tablets**

About 50 gm of Mini tablets were coated by mixing with single unit tablets to avoid the expulsion from coating pan during coating. The method was same as the above.

TWG (tablet weight gain) =Final weight – Initial weight / Initial weight *100

**Evaluation of Metronidazole tablets**

**Physicochemical characterization of tablets**

The developed formulations were assessed for physico-chemical characteristicssuch as weight variation, thickness, friability, hardness, and assay.

The Metronidazole tablets and multiple units (capsules containing 3mm tablets) were evaluated for its *in vitro* dissolution study. The *in vitro* release of drug was studied with basket apparatus (USP type I apparatus). In this studies, slight modifications with addition of another pH medium, based on different transit time present from stomach to colon, were carried out with different pH conditions similar to *in vivo* conditions (pH 1.2 for 2 hrs, pH 6.8

for 3 hrs and pH 7.4 for 19 hrs) were maintained for the entire study. 900 ml of 0.1 N HCl was taken in a vessel, formulation was kept in basket after the media attained the temperature of 37 ± 0.5$^{o}$C. The basket rpm was maintained at 50. 5ml of sample was withdrawn at specific time interval and replaced with a particular medium. After 2 hrs, the 0.1 N HCl was discarded and replaced with pH 6.8 phosphate buffer and it was maintained for 3 hrs after that pH 7.4 phosphate buffer was used for remaining 19 hrs.

**Evaluation of release rate kinetics**

The release rate kinetics mechanism of the designed dosage forms analysed by fitting the data intofirst order, zero-order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics, First order release rate kinetics,Higuchi release model, Korsmeyer and Peppas release model,*In vivo* X-ray studies.

To monitor the tablets throughout the GIT, X-ray imaging technique or Roentgenography was used by the insertion of radio-opaque material into the dosage form enables it to be tracked by X-rays. Barium sulphate is employed to follow the movement, location and integrity of the dosage form after oral administration by monitoring the test subject under a fluoroscope and taking a series of X-rays at different set of intervals.

Three healthy male volunteers, between 22-25 years and 50-70 kg body weight, were contributed in *in vivo* studies. Each subject ingested with barium sulphate tagged tablets orally, after an overnight fast. The tablets were visualized andabdominal X-ray radiographs were taken after specific time points.

## RESULTS AND DISCUSSION

**FT-IR Spectroscopy**

FT-IR analysis of the samples of Metronidazole, physical mixture of Metronidazole and Eudragit S-100, physical mixture of Metronidazole and Eudragit L-100, Optimised formulations ES11 and EL13 were conducted by KBr Plate method and spectrum was collected within the region 4,000–400 cm$^{-1}$.

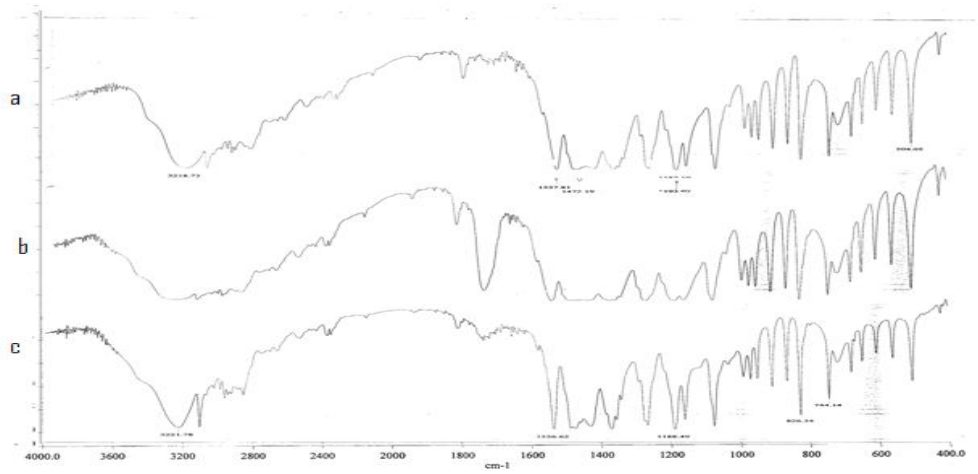



**Figure. FT-IR spectra of Metronidazole (a); physical mixture of Metronidazole and Eudragit S-100 (b); and the formulation ES11 (c).**

As seen in figure.6 Metronidazole exhibited peaks at 3174.1, 1536.9, 1361, and 1269.5 cm-1. The FTIR spectra of the physical mixture of Eudragit S-100 and optimised formulation ES11 showed the same absorption bands as the pure drug, illustrating absence of interaction between drug and the excipients and polymers used.

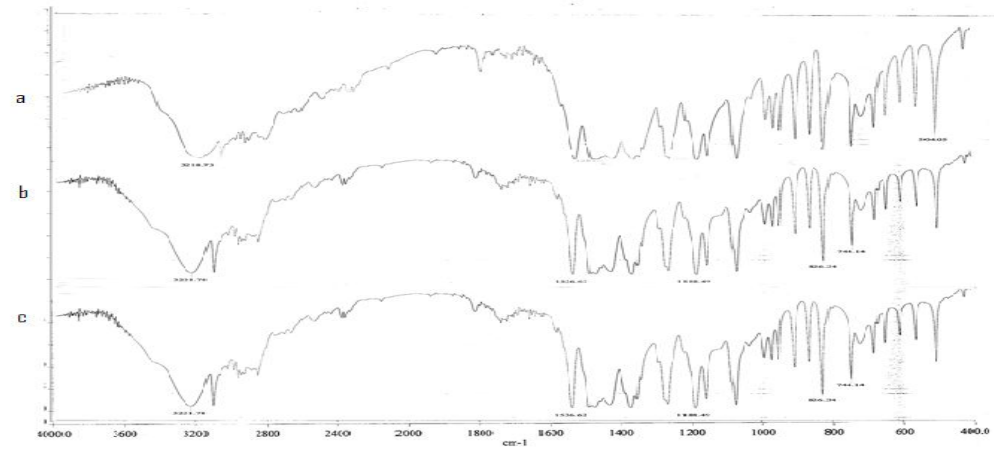



**Figure: FT-IR spectra of Metronidazole (a); physical mixture of Metronidazole and Eudragit L-100 (b); and the formulation EL13 (c).**

As seen in figure.7 Metronidazole exhibited peaks at at 3174.1, 1536.9, 1361, and 1269.5 cm-1. The FTIR spectra of the physical mixture of Eudragit L-100 and optimised formulation EL13 showed the same absorption bands as the pure drug, illustrating absence of interaction between drug and the excipients and polymers used.

| | Percentage w/w | | | | |
|---|---|---|---|---|---|
| Ingredients | TF1 | TF2 | TF3 | TF4 | TF5 |
| Metronidazole | 500 | 500 | 500 | 500 | 500 |
| HPMC K4M | - | 15 | 20 | 25 | 35 |
| Avicel PH 101 | 100 | 85 | 80 | 75 | 65 |
| Talc | 10 | 10 | 10 | 10 | 10 |
| Magnesium stearate | 5 | 5 | 5 | 5 | 5 |
| Water | q.s | q.s | q.s | q.s | q.s |

The apparent bulk density values ranged from 0.4521 to 0.4693 respectively. The evaluated values of angle of repose and carr's index in %ranged from 20.40 ± 2.15 to 28.91 ±1.35 and 15.41 ± 1.14 to 19.35 ± 1.25 respectively and indicates good to fair flow properties of the formulated granules.

**Evaluation of tablets**

**Table. Cumulative percent drug release of Metronidazole core tablets in SGF (pH 1.2), SIF (pH 6.8), and SIF (pH 7.4).**

| Time (min) | pH - 1.2 | pH - 6.8 | pH - 7.4 |
|---|---|---|---|
| 0 | 0 | 0 | 0 |
| 5 | 15.14 ± 1.45 | 28.31 ± 2.26 | 35.46 ± 1.84 |
| 10 | 24.63 ± 2.37 | 49.65 ± 2.15 | 56.83 ± 1.53 |
| 15 | 30.78 ± 2.15 | 72.46 ± 2.43 | 78.98 ± 2.17 |
| 20 | 38.12 ± 2.04 | 84.35 ± 1.06 | 89.46 ± 1.38 |
| 30 | 46.96 ± 1.48 | 95.24 ± 2.08 | 97.25 ± 2.72 |
| 45 | 55.78 ± 2.06 | 98.68 ± 1.57 | 98.94 ± 1.25 |
| 60 | 65.28 ± 1.82 | 99.32 ± 1.49 | 100.83 ± 1.46 |
| 75 | 75.64 ± 1.98 | - | - |
| 90 | 81.81 ± 2.79 | - | - |
| 120 | 91.53 ± 1.08 | - | - |
| 150 | 96.46 ± 3.05 | - | - |
| 180 | 100.15±2.58 | - | - |

Data represents mean ± SD, n = 3

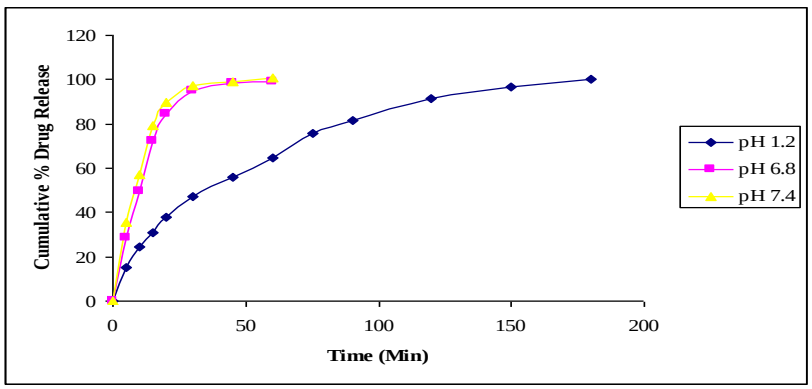



**Figure. Dissolution profile of Metronidazole core tablets in SGF (pH 1.2), SIF (pH 6.8), and SIF (pH 7.4).**

**Metronidazole mini tablets characteristics:** The core and coated mini tablets were evaluated for hardness, thickness, weight variation, Friability, assay.

**Table. Physical properties of Metronidazole mini tablets**

| Formulation | Thickness (mm) | Hardness ($kg/cm^2$) | Weight variation (mg) | Friability (%) | Assay (%) |
|---|---|---|---|---|---|
| core tablet | 1.2 ± 0.2 | 3.2 ± 0.4 | 31 ± 1.5 | 0.7 | 102.4± 0.91 |
| ES11 | 1.8 ± 0.4 | 3.8 ± 0.5 | 32.7 ± 0.8 | 0.3 | 99.8± 0.53 |
| EL13 | 1.8 ± 0.3 | 3.7 ± 0.5 | 32.5 ± 0.9 | 0.3 | 100.5 ± 0.12 |

**Dissolution results of coated Metronidazole tablets:** The percentage of drug released from single unit and multiple unit tablets (mini tablets) coated with ES-100, EL-100 and EC were calculated. The percentage drug release from ES11a (5% TWG), ES11b (10% TWG), ES11c (15% TWG), and ES11d (20% TWG) was given in Table.

**Dissolution results of ES11 tablets**

**Table Percentage drug release from different % TWG of ES11 tablets**

| pH | Time | ES11a | ES11b | ES11c | ES11d |
|---|---|---|---|---|---|
| 1.2 | 0.5 | 0.13 ± 1.98 | 0.12 ± 2.57 | 0.14 ± 2.43 | 0.13 ± 1.52 |
| | 1 | 0.14 ± 1.45 | 0.14 ± 1.84 | 0.15 ± 2.11 | 0.16 ± 1.46 |
| | 2 | 0.15 ± 2.69 | 0.16 ± 2.13 | 0.16 ± 1.3 | 0.16 ± 2.34 |
| 6.8 | 3 | 13.32 ± 1.53 | 8.43 ± 2.35 | 4.56 ± 2.34 | 2.95 ± 1.73 |
| | 4 | 17.43 ± 1.84 | 13.56 ± 1.62 | 8.01 ± 2.16 | 4.54 ± 2.62 |
| | 5 | 23.84 ± 1.78 | 18.18 ± 1.09 | 12.87 ± 1.06 | 4.98 ± 1.38 |
| 7.4 | 6 | 35.57 ± 2.85 | 31.26 ± 2.48 | 25.63 ± 1.84 | 17.97 ± 2.41 |
| | 8 | 46.65 ± 2.02 | 40.31 ± 1.73 | 35.96 ± 1.47 | 29.42 ± 2.02 |
| | 10 | 55.94 ± 2.71 | 49.56 ± 1.62 | 45.32 ± 2.54 | 41.93 ± 2.53 |
| | 12 | 66.23 ± 2.38 | 60.89 ± 2.45 | 55.46 ± 1.63 | 50.97 ± 1.08 |
| | 18 | 85.34 ± 1.36 | 81.76 ± 2.38 | 78.56 ± 1.24 | 74.34 ± 2.51 |
| | 24 | 99.95 ± 2.53 | 99.92 ± 1.86 | 99.90 ± 2.64 | 98.92 ± 1.85 |

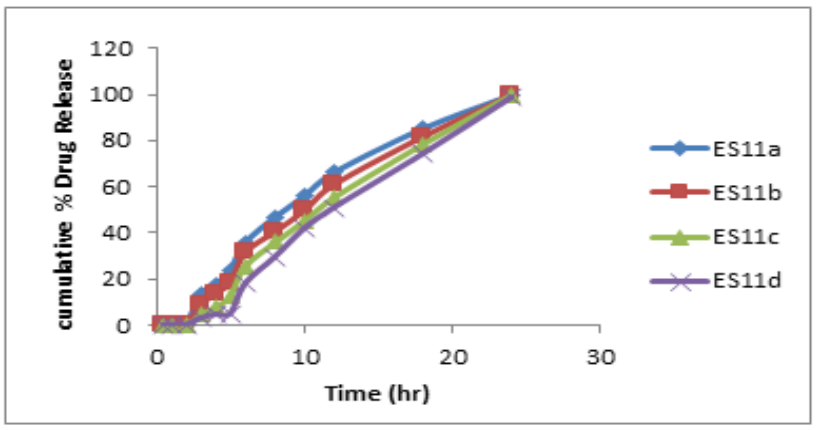



**Figure. Dissolution profile of different % TWG of ES11 tablets.**

From the graph, it was detected that all the formulations were successfully able to prevent drug release in pH 1.2 buffer. However drug release for ES11a, ES11b and ES11c was found to occur in pH 6.8 buffer. ES11a, ES11b, and ES11c showed 23%, 18%, and 12%, release at 5$^{th}$ hr. Whereas ES11d showed good lag time of 5 hrs and it releases very little amount at 5$^{th}$hr (4.98%). However only ES11d was able to retard the release in pH 6.8 buffer and showed significant release (>17%) in pH 7.4 buffer at 6 hrs. Hence ES11d i.e., Core tablets coated with 20% TWG of ES-100 was found to be successful in releasing drug at colonic pH.

**Dissolution results of ES11 mini tablets**

**Table. Percentage drug release from ES11 mini tablets.**

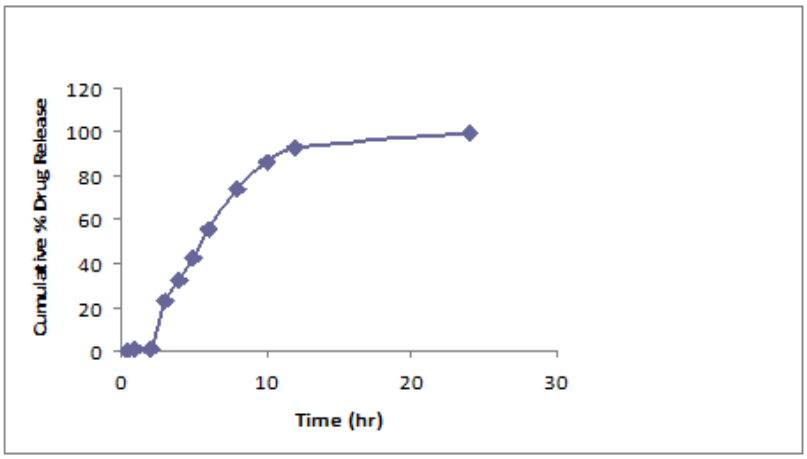



**Figure. 13. Dissolution profile of ES11 mini tablets.**

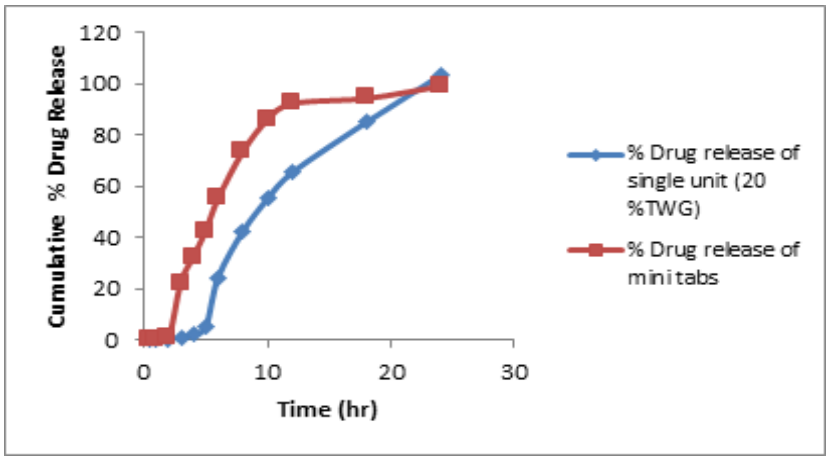



**Figure.14 Comparison of release profile of ES11 tablets and mini tablets.**

Mini tablets of ES11 were able to prevent drug release at gastric pH but were not able to do so in pH 6.8 buffer. The mini tablets showed drug release in pH 6.8 buffer at 3$^{rd}$ hour. Thus, ES11d were preferred over mini tablets.

**Dissolution results of EL13 tablets**

**Table. Percentage drug release from EL13 tablets.**

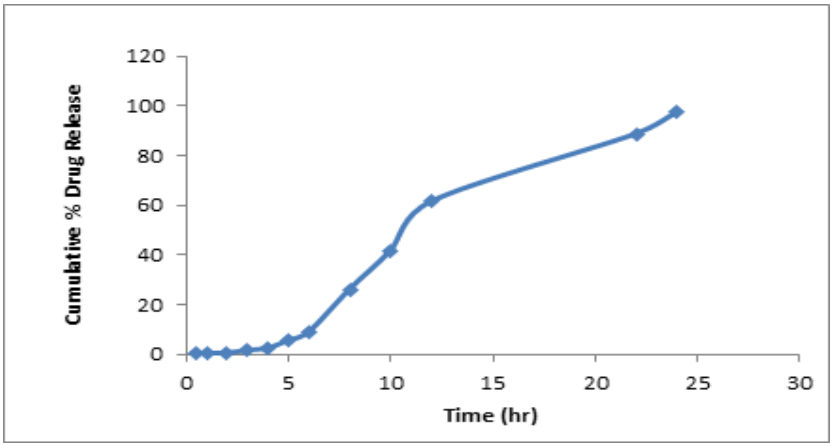



**Figure. Dissolution profile of EL13 tablets.**

**Dissolution results of EL13 mini tablets:** The 5% TWG of EL-100 coated mini tablets were subjected to dissolution and the cumulative percentage drug release was shown in Table.26

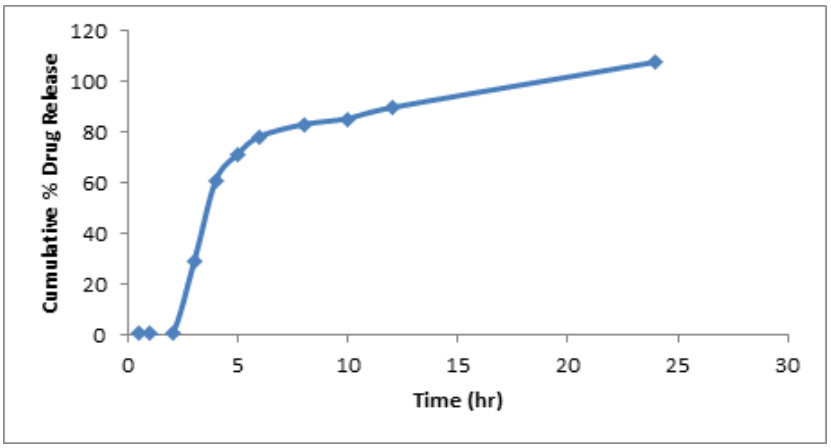



**Figure. Dissolution profile of EL13 mini tablets.**

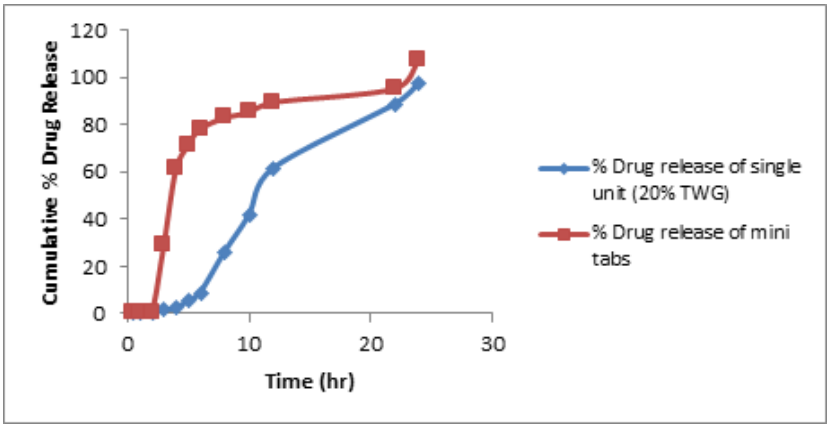



**Figure. Comparison of release profile of EL13 tablets and mini tablets.**

Although both EL13 tablets and mini tablets showed no release in SGF, mini tablets showed rapid release of drug in pH 6.8 phosphate buffer while EL13 tablets showed less release. Hence the release of drug from EL13 tablets was less in pre-colonic conditions when compared to that of mini tablets; it was assumed that Eudragit L-100 20% TWG (ES13) coated tablets were superior to mini tablets.

**Dissolution results of ECS14 tablets**

The 20% TWG of EC and ES-100 coated Metronidazole tablets were subjected to dissolution and the cumulative percentage drug release was shown in Table.

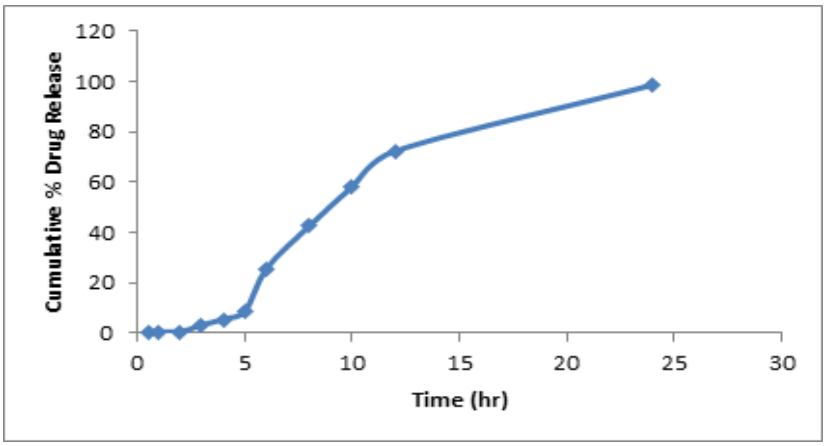



**Figure. Dissolution profile of ECS14 tablets.**

**Dissolution results of ECL15 tablets**

The 20% TWG of EC and EL-100 coated Metronidazole tablets were subjected to dissolution (15% TWG of EC primary coating over that 5% TWG of EL-100 coating) and the cumulative percentage drug release was shown in Table.28.

**Table. Percentage drug release from ECL15 tablets.**

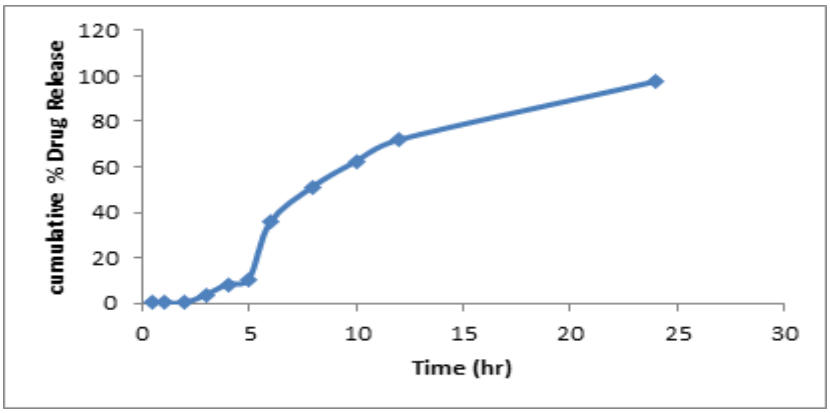



**Figure. Dissolution profile of ECL15 tablets.**

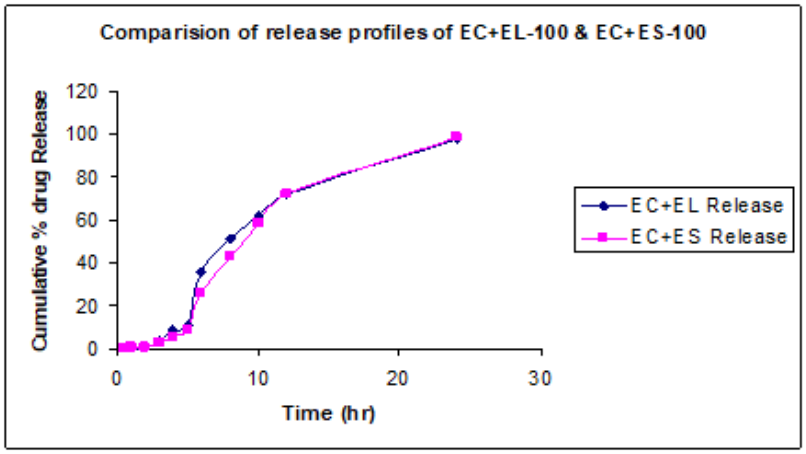



**Figure. Comparison of release profile of ECS14 tablets and ECL15 tablets.**

ECL15 tablets were precoated with 15% TWG of EC and then last coat with 5% TWG of EL-100. ECS14 tablets were precoated with 15% TWG of EC and then final coat with 5% TWG of ES-100. It was observed that both the formulations performed well and showed an initial lag time of 5 hrs. However release of drug from ECL15 was found to be a little more by about 10% in pH 6.8 when compared to ECS14. Hence ECS14 tablets were performing better when compared to ECL15 tablets.

**Kinetic results**

The drug release kinetics and mechanism of release of Metronidazole is determined by the application of zero order, first order, Higuchi, and korsmeyer- peppas kinetics as tabulated in Table 29. The $r^2$ values are 0.9767, 0.9453, and 0.9303 for all three optimized formulations ES11, EL13 and ECS14 respectively as they are following the zero-order release.

According to Korsmeyer–Peppas models, their $r^2$ values fairly accommodated in the range of 0.8054–0.8567 with n value above 1, the mechanisms of drug release was non-fickian diffusion (super case-II). From this model it implies that the release of drug dependent on swelling, relaxation and rate of erosionof polymer with zero order release kinetics.

**Table. 29. Drug release kinetics.**

| Formulatoin code | Zero order | First order | Higuchi | Korsmeyer&peppas | Peppas(n) |
|---|---|---|---|---|---|
| ES11 | **0.9767** | 0.8643 | 0.8499 | 0.8326 | 1.1374 |
| EL13 | **0.9453** | 0.9107 | 0.8155 | 0.8054 | 1.1017 |
| ECS14 | **0.9303** | 0.9118 | 0.8683 | 0.8567 | 1.7186 |

***In-vivo* X-Ray Studies**

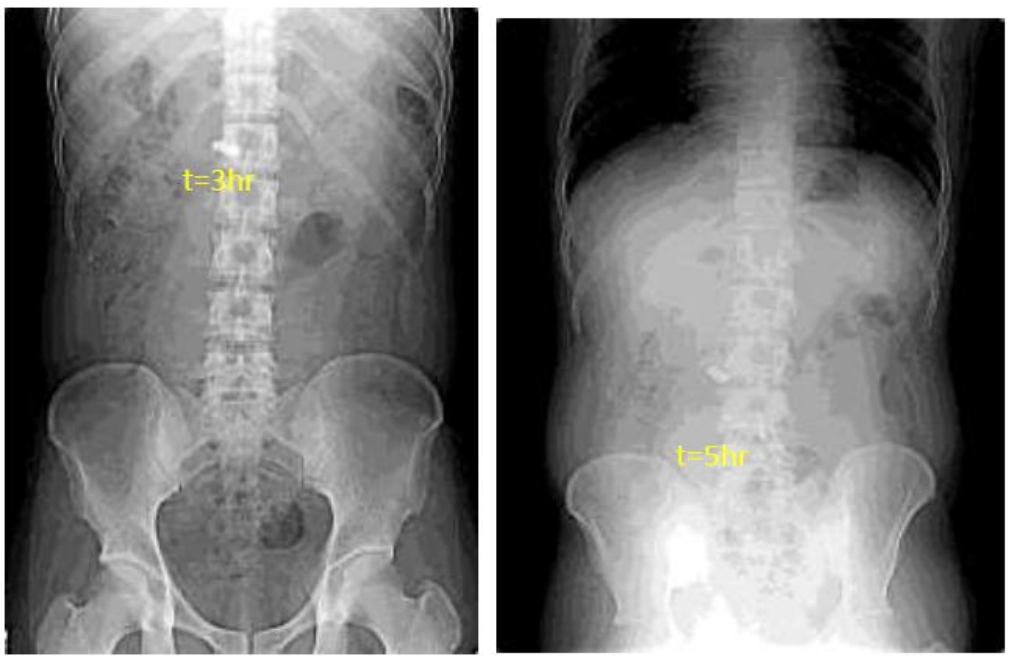
X-ray studies were performed to estimate the efficiency of the delivery system *in vivo.* 25% of the drug in the core tablet was replaced with a radiopaque substance i.e., $BaSO_4$ and the Coated with Eudragit S-100 solution till a total weight Gain of 20% was observed. These tablets were administered to three healthy male volunteers. X-rays were taken at different times after administration of tablets to determine its location.

**Table. Composition of core tablet for X-ray studies.**

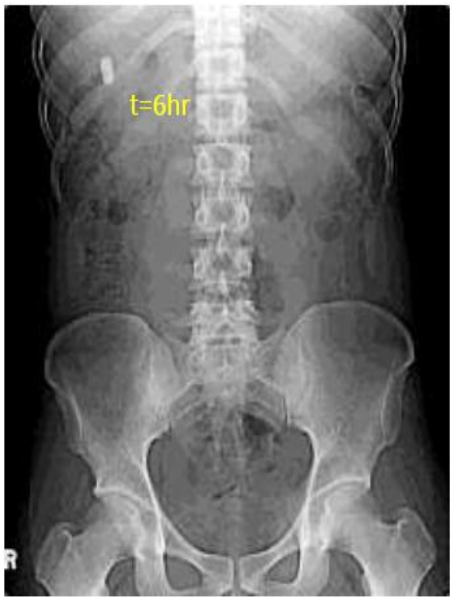
| Ingredient | Amount(mg/tablet) |
|---|---|
| Metronidazole | 500 mg |
| Barium sulphate | 125 mg |
| HPMC K4M | 35 mg |
| Microcrystalline cellulose | 65 mg |
| Talc | 10 mg |
| Magnesium stearate | 5 mg |

*In vivo* residence time evaluation by X-rays in human volunteers showed that the formulation reached the ascending colon intact after 6 hrs while disintegration completed after 10 hr.

**X- Ray photographs of volunteer** I




**After 3 hour of ingestion** **B) After 5 hour of ingestion**




**C) After 6 hour of ingestion.**

I A) X-ray was taken after 3 hour of ingestion showing the location of the formulation in the duodenum.

I B) X-ray was taken after 5 hour of ingestion showing the location of the formulation in the ileum.

I C) X-ray was taken after 6 hour of ingestion showing the location of the formulation in the ascending colon.

## CONCLUSION

From the practical results it was concluded that TF 5 containing core tablet composition was optimized. TF5 tablets were used for the coating of all (EC1 to ECL15) coating solutions. The tablets coated with ethyl cellulose failed to retain the coating at 3 hour of media change (pH 6.8). The coat was floated on the media without disintegration. It was not sticking to the core tablet due to hydration. The tablets coated with ES11, EL13, ECS14 coating solutions were optimized. They showed the lag time of 5 hours and drug was released less than 10% at 5 hour. The single unit tablets showed better results over multiple unit tablets. This is because the multiple unit tablets got less percentage of coating than the single units. The multiple units were coated in conventional coating pan along with the single unit tablets at 15 psi of atomizing air pressure. However the multiple units suffered expulsion from the coating pan if they are coated alone at 15 psi of air pressure. Hence they were coated at low atomizing pressures to prevent the expulsion. But the coating solution was not atomized at low

pressures. Hence the single unit tablets proved better over multiple units coated in conventional coating pan.

The EC1 to EC8 coated tablets were failed to retain the coating. Hence the attempts were made to improve the EC coating with combination of ES-100 and EL-100. The tablets coated with ECS14 coating solution shows 5 hour lag time out of all EC containing formulations. This is because of 15 %TWG of EC coating (primary coating) and 5 % TWG of ES-100 (secondary coating). The outer most ES-100 layer protects the formulation from earlier peel off problem in 6.8 pH phosphate buffer.

The 20% TWG ES-100 tablets (with $BaSO_4$) were subjected to *in vivo* X-ray studies shows that the formulation reached ascending colon within 6 hour and it was disintegrated after 10 hour.

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