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Formulation and Evaluation of Misoprostal by Chronotherapeutic Drug Delivery System

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Abstract

In this present study it has been aimed to develop Spray Coated tablets of Misoprostol with a view of minimizing the drug release in the physiological ecology of stomach and small intestine and to ensure maximum drug release in the colon. This study was conducted to develop colon targeted Misoprostal delivery for the treatment of Colonic Bacterial Infections and to study the influence of coating thickness and ratios of lag time polymers (Eudragit L 100 and Eudragit S 100) on drug release and lag time.

Introduction

Chronotherapy can be defined as the administration of bio-active agent or pharmaceutical products at certain periods of the day that are thought to reduce undesirable adverse effects to increase the drug's desired effects. The study of biological rhythms and their respective mechanisms is known as Chronobiology.

On the basis of biological response of time keeping, the Biological rhythm plays an important role in determining the response of drugs administered at any time of the day [1]. Many approximations have been done, in order to enhance the effectiveness of the drug, one of the method used is Chronotherapeutic Drug delivery system.

These differences can cause changes both in abnormal condition and in plasma drug concentrations. Human circadian rhythm is based on the activity of sleep cycle, human genetic makeup influences the sleep activity cycle and hence, the functions of the body is also affected [2] Chronopharmaceutical Drug Delivery Systems (ChrDDS) can be defined as regardless of the route of administration, the ability of the bio-active compound or therapeutic agent to deliver its desired effects to a patient in a diseased condition and should embody or includes time-controlled and to deliver the drug to specific site [3,4].

The main goal of Drug Delivery Research is to develop formulations in order to meet the therapeutic needs for particular pathological conditions. The importance of Biological Rhythms in chronotherapy has been demonstrated in the research of Chronopharmacological field and this brought a new approach to development of Drug Delivery System [5].

Biological Rhythms

Biological rhythm are basic characteristic of human life on earth that is explained as Cyclical Activities or self-sustaining oscillation of human and animal origin [9]. The spectrum of biological rhythms is well displayed and understood in Table 1. A great deal of research shows that the inherited period of the human pacemaker clock is not precisely 24 hours [6]. In fact, in most people, it is somewhat longer, closer to 25 hour Figure 1. Environmental times, termed synchronizers or zeitgebers, the strongest one being the daily light–dark cycle occurring in conjunction with the wake–sleep routine, set the inherited pacemaker circadian timekeeping systems to 24 hours each day [7,13].

Cardiac Rhythms

This is the most common biological rhythm and it deals with biological functions of human which can be represented as such of 24 hours clock and it also alter the sleep-wake cycle Figure 2. The circadian rhythms of serum cholesterol and triglycerides and urinary diuresis crest early in the evening. [8]. The information conveyed in this figure clearly illustrates that the biochemistry and physiology of human beings are not constant; rather, they are variable in predictable and coordinated manner during the 24 h [12,13].

Chronotherapy

Coordinating biological rhythms with medical treatment is

Table 1: List of materials used:

Name of the material	**Source**
Misoprostol	Natco pharma India.
Ethyl Cellulose	Signet Chemical Corporation, Mumbai, India.
Eudragit L-100	Merck Specialities Pvt Ltd, Mumbai, India.
Eudragit S-100	Merck Specialities Pvt Ltd, Mumbai, India.
Eudragit RSPO	Merck Specialities Pvt Ltd, Mumbai, India
Hydroxy Propyl Methyl Cellulose K100M	Merck Specialities Pvt Ltd, Mumbai, India
Isopropyl alcohol	Universal Chemicals, Hyderabad, India
Reagents	
Hydrochloric Acid	Universal Chemicals, Hyderabad, India.

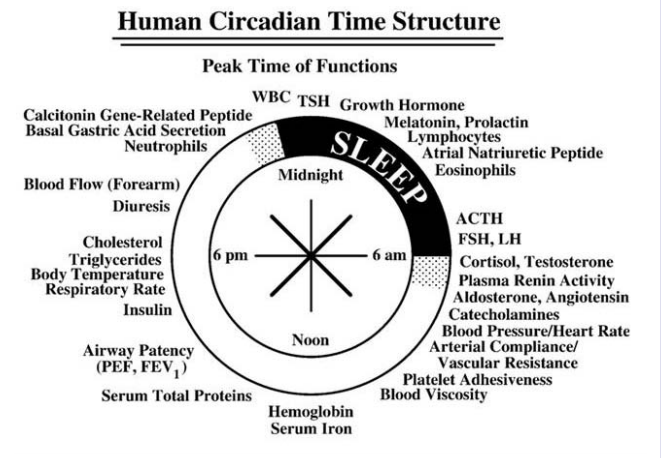


Figure 1: Human circadian time structure. Shown is the approximate peak time of circadian (24-h) rhythms of selected biological variables in persons adhering to a normal routine of daytime activity (~6–7 a.m. to ~10–11 p.m.) alternating with nighttime sleep.

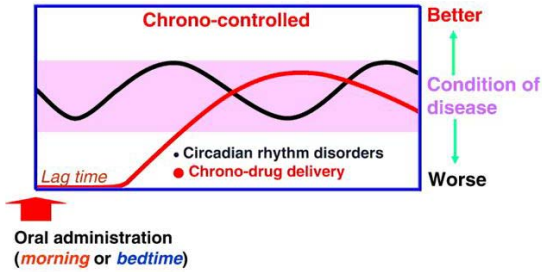


Figure 2: Circadian rhythm of clinical diseases.

known as Chronotherapy, which allows for appropriate dosing of actives at the most suitable times of the day, thus improving efficacy and reducing undesirable side effects [10,11].

Advantages of Chronotherapy:

- Important advantage of Chronotherapy is that it is drug-free treatment
- Enhancement of Chronotherapy takes places when is a person is sleeping.
- The disease condition and confidence is improved when patients often fall asleep during Chronotherapy.
- Chronotherapy has beginning, middle and an end for the treatment, this makes chronotherapy different from other treatment processes. So it is easily predictable the point at which the treatment works.
- It gives the patient an entire new schedule like waking up earlier and sleeping prior to scheduled time which will be quite unusual for some days but it will give u a period to adjust psychologically [16].
- Chronotherapy improves stability
- Chronotherapy has no risk of dose dumping [19].

Disadvantages of Chronotherapy:

- A non 24 hour sleep- wake syndrome is developed after the Chronotherapy treatment as sometimes the person sleeps or over 24 hours during the treatment.
- The person will wake up earlier then the scheduled time and he/she will not be able to sleep again.
- Chronotherapy makes the person to become less productive during the therapy and staying awake till the other schedule will be bit uncomfortable.
- It is mandatory to have Medical supervision during this therapy.
- Large number of process variables.
- Manufacturing requires only Trained /skilled person.

Chronotoxicology

Chronotoxicology is an important aspect of chronodynamics; it refers to the interactions between the toxic substances and biological rhythms [18]. It deals specifically with the rhythm-dependent, and refers with the major and minor differences in the indication and severity of adverse effects and the patients suffering with the intolerance to medications or pharmaceutical compound [14]. The high risk of adverse effects and relatively narrow therapeutic range for the classes of medications in particular, are likely to show significant dosing-time differences in safety [17].

When ingested in the morning as a single daily dose at the commencement of the daily activity span, these medications are best tolerated because of their least adrenocortical suppression. Especially in the evening between dinner and bed time, when the moderate daily dose of glucocorticoid is ingested or inhaled late in the day, the risk of adrenocortical suppression is increased [15].

Materials

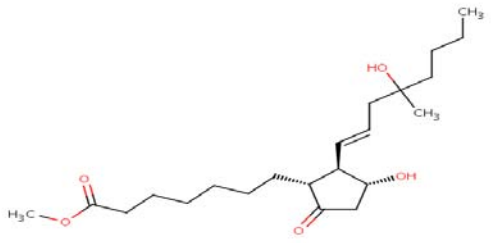
Drug : **MISOPROSTOL**

Solubility : Water soluble >1.6mg/mL at 25.0° C

Physical State: Liquid

Melting point: 261-263°C

CAS Registry No.: 62015398



Molecular formula: $C_{22}H_{38}O_5$

Molecularweight: Average:382.5341 , Mono isotopic: 382.271924326

Bioavailability: 80%- 85%

Half-life: 20-40 minutes

Protein binding: 80-90%

Dose : 100-200mcg

Category:

- Preventing stomach ulcers (duodenal, gastric and NSAID induced)
- Inducing labor
- End a pregnancy (abortion)
- Spontaneous abortion
- Postpartum Hemorrhage (PPH)
- Uterine rupture

The following are the materials and tables used. Table 1 and Table 2

Methods

Buffers used for Standard calibration curve for Misoprostol

Preparation of 0.1N Hydrochloride: 0.1N HCl is prepared by dissolving 8 ml of Hydrochloric acid (conc.) make upto 1000 ml with Distilled water.

Preparation of simulated Intestinal fluid (pH 7. 4 Buffer): Simulated Intestinal Fluid (pH 7.4 Buffer) is prepared by dissolving 50 ml of 0.2M Potassium Dihydrogen Ortho Phosphate and 39.1 ml of 0.2M Sodium Hydroxide and make the volume upto 200 ml with Distilled water.

Preparation of 6.8p H Buffer: By dissolving 50ml of 0.2M Potassium Dihydrogen Ortho Phosphate and 22.4 ml of 0.2M Sodium Hydroxide and make up the volume upto 200ml with Distilled water gives 200ml o f pH 6.8 Buffer.

Preparation of 0.2 M potassium Dihydrogen Ortho Phosphate: Dissolve 27.218 o f Potassium dihydrogen ortho phosphate in Distilled water and make up to 1000ml with Distilled water.

Preparation of 0.2 M Sodium hydroxide: Dissolve 8.0gm of Sodium hydroxide in Distilled water and make up to 1000ml with Distilled water.

Analytical Method

Determination of Absorption Maxima: A solution of Misoprostol of concentration 10 µg/ ml was prepared in 0.1NHCl, 7.4 PH & phosphate buffer 6.8PH respectively, UV spectrum was taken using Double beam UV/VIS spectrophotometer. The solution was scanned in the range of 200 – 400.

Table 2: List of Equipments Used

Name of the Equipment	Model	Manufacturer
Weighing Balance	Dona balance (KM2)	Keroy Scientifics, India.
Tablet Compression Machine (Multistation)	Mini –Press	Karnavati Engg Pvt Limited, India.
Hardness tester	Monsanto	Sisco, Mumbai, India.
Vernier callipers	VC03	Mitutoyo, Japan.
Roche Friabilator	FT 1020	Lab india , Mumbai, India
Auto Dissolution Apparatus	8500	Lab india , Mumbai, India
UV-Visible Spectrophotometer	UV 3000 plus	Lab india , Mumbai, India
pH meter	PNo.9251117	Lab india , Mumbai, India
FT-IR Spectrophotometer	Spectrum 65	Per kin Elmer, United States of America.
Pharma R&D Coater	GMP	VJ Instruments limited.

Preparation Calibration Curve: For Misoprostol: 10mg of Misoprostol drug was accurately weighed and dissolved in 10ml of 0.1N HCl, 7.4 PH, and 6.8 PH in 10 ml volumetric flask , to make (1000 µg/ml) standard stock solution (1). Then 1 ml stock solution (1) was taken in another 10 ml volumetric flask to make (100 µg/ml) standard stock solution (2), then again 1 ml of stock solution (2) was taken in another 10 ml volumetric flask and then respective concentrations were prepared such as 2, 4,6, 8, 10, 12, 14, 16, 18 ,and 20µg/ml with 0.1N HCl, 7.4 PH, and 6.8 PH respectively. The absorbance of standard solution was determined using UV/ VIS spectrophotometer at 273nm. Linearity of standard curve was assessed from the square of correlation coefficient (r2) which determined by least-square linear regression analysis.

Preparation of Misoprostol core tablets: Each core tablet (average weight 400 mg) for *in vitro* drug release studies consist of Misoprostol, Ethyl cellulose, Eudragit RSPO, HPMC K 1OO M, HPMC E 15, Talc, Lactose and Magnesium stearate, Dicalcium phosphate (Table 5).The materials were weighed accurately, mixed and passed through a mesh no 60 to ensure complete mixing. The thoroughly mixed materials were then directly compressed into tablets using 12 mm round, flat punches on a tablet punching machine.

Tablet quality control tests such as weight variation, hardness, friability, thickness, and dissolution in different media were performed on the core tablets Table 3.

Coating of Misoprostol core tablets: The optimized core tablets (F5 and F6) were spray coated with different quantities of coating material containing of Eudragit L 100 and Eudragit S 100 in different ratios such as 1:1, 1:2, 2:1 in different concentrations like 5 %, 7.5 % with R&D Coater, VJ Instruments. Tablet quality control tests were performed on the compression coated tablets Table 4.

Evaluation of Tablets

The designed formulations of core and compression coated

Misoprostol tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

Weight Variation Test: To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The mean and deviation were determined. The percent deviation was calculated using the following formula. Table 5

% Deviation = (Individual weight – Average weight / Average weight) × 100

Hardness: Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated.

Thickness: Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation Table.

Friability: The mechanical strength of tablets is called as Friability. Roche friabilator was used to determine the friability. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were reweighed; loss in the weight of tablet is the measure of friability and is expressed in percentage as

% Friability = [(W1-W2)/ W] × 100

Where,

W1= Initial weight of three tablets

W2= Weight of the three tablets after testing [20,21].

Determination of Drug Content: Both the core tablets and compression-coated tablets of Misoprostol were tested for their drug content. Ten tablets were finely powdered, the quantities of the powder equivalent to one tablet weight of Misoprostol were accurately weighed, and transferred to a 100 ml volumetric flask containing 50ml water and were allowed to stand to ensure complete solubility of the drug. The mixture was made up to the volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectro photometer. The drug concentration was calculated from the calibration curve.

In vitro drug release studies

Drug release studies of Misoprostol core tablets: The core tablets containing 400mg of Misoprostol were tested in 6.8 pH phosphate buffer solution for their dissolution rates. Dissolution studies were performed using USP dissolution apparatus 2, with50 rpm, at 37±0.5°C. At various time intervals, a sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at 320 nm.

Table 3: Compostion of Core Tablets

SS.NO	Ingredients	Quantity/tablet(mg)					
		Formulation codes					
		F1	F2	F3	F4	F5	F6
11	Misoprostol	200	200	200	200	200	200
22	HPMCK 100M	50	100	-	-	-	-
33	HPMC E15	-	-	50	100	-	-
44	Ethyl cellulose	-	-	-	-	50	100
55	Lactose	138	88	138	88	138	88
66	Magnesium stearate	4	4	4	4	4	4
77	Talc	8	8	8	8	8	8
	Total Weight of tablet(mg)	400	400	400	400	400	400

Table 4: Composition of coating solution of Coated Tablets

Ingredients	5%			7%		
	1:1	1:2	2:1	1:1	1:2	2:1
Eudragit L 100(mg)	2.5mg	1.7mg	3.4mg	3.75mg	2.5mg	5mg
Eudragit S 100(mg)	2.5mg	3.4mg	1.7mg	3.75mg	5mg	2.5mg
Isopropyl alcohol(ml)	90ml	90ml	90ml	87.5ml	87.5ml	87.5ml
Dibutylthalate(ml)	1ml	1ml	1ml	1ml	1ml	1ml
Talc	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg	0.5mg
Water(ml)	3ml	3ml	3ml	3ml	3ml	3ml
Total (percentage)	100	100	100	100	100	100

Table 5: Pharmacopoeial specifications for Tablet Weight Variation.		
Average weight of tablet (mg) (I.P)	**Average weight of tablet (mg) (U.S.P)**	**Maximum percentage difference allowed**
Less than 80	Less than 130	10
80-250	130-324	7.5
More than	More than 324	5

The dissolution results of Misoprostol core tablets in SIF (pH 7.4) solutions were shown in Table. From the above drug release profiles of core tablets it was interpreted that among all the formulations, formulations such as F5and F6 with Ethyl cellulose: Misoprostol ratio (1:2 and 1:4) has shown 91.29 ± 0.39 % and 94.09 ± 0.30 % drug release respectively. These were subjected to spray coating using enteric coating polymers such as Eudragit L 100 and Eudragit S 100 [22].

Drug Release Studies of Spray Coated Misoprostol Tablets: The release of Misoprostol from coated tablets was carried out using USP paddle - type dissolution apparatus at a rotation speed of 50 rpm, and a temperature of 37±0.5 °C. For tablets, simulation of gastrointestinal transit conditions was achieved by using different dissolution media. Thus, drug release studies were conducted in simulated gastric fluid (SGF, pH 1.2) for the first 2 hours as the average gastric emptying time is about 2 hours. Then, the dissolution medium was replaced with enzyme- free simulated intestinal fluid (SIF, pH 7.4) and tested for drug release for 3hours, as the average small intestinal transit time is about 3 hours, and finally enzyme-free simulated intestinal fluid (SIF, pH 6.8) was used up to 12 hours to mimic colonic pH conditions [23].

Drug release was measured from spray coated Misoprostol tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples with drawn at various time intervals were analyzed spectro photo metrically at 275nm and 270nm respectively. All dissolution runs were performed for six batches. The results were given with deviation [24,25,26].

Results

Analytical Method

Graphs of Misoprostol was taken in Simulated Gastric fluid (pH 1.2) and Simulated Intestinal Fluid (pH 6.8 and 7.4)

Graph of Misoprostol in 0.1N HCl (275nm) Table 6 and Figure 3

Graph of Misoprostol in 7.4 pH Simulated Intestinal Fluid (319nm) Graph 1 Figure 4 and Table 7

Preformulation Parameters of Core Material Table 8

Misoprostol blend was subjected to various pre-formulation parameters. The apparent bulk density and tapped bulk density values ranged from 0.52 to 0.581 and 0.606 to 0.671 respectively. According to Tables 3 and 4, the results of angle of repose and compressibility index (%) ranged from 32.74±0.12 to 37.08 ± 0.96and 13.37±0.38to 14.72±0.62 respectively. The results of angle of repose (<35) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. These results show that the core powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Table 6: Observations for graph of Misoprostol in 0.1N HCl	
Conc. [mg/l]	**abs**
0	0
2	0.145
4	0.319
6	0.482
8	0.681
10	0.858

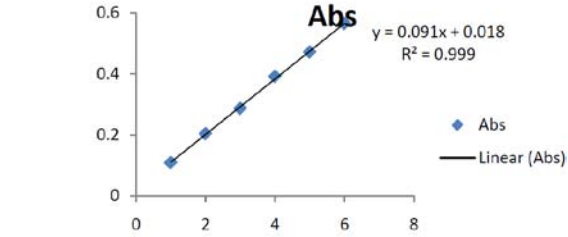


Figure 3: Standard graph of Misoprostol in 0.1N HCl.

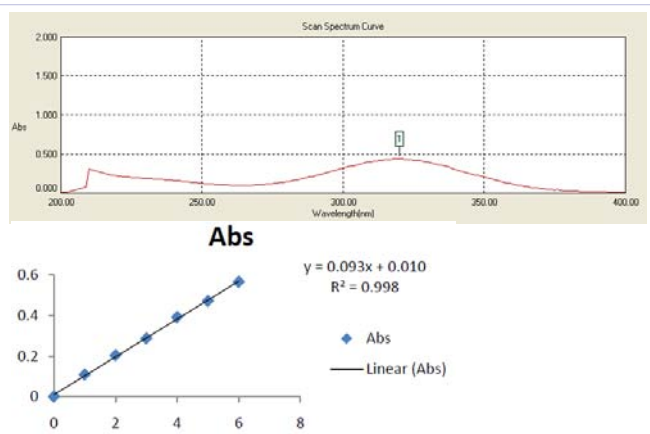


Figure 4: Standard graph of Misoprostol in 7.4 pH.

Table 7: Observations for graph of Misoprostol in 7.4 pH	
Conc. [mg/l]	**Abs**
0	0
1	0.109
2	0.204
3	0.287
4	0.392
5	0.472
6	0.566

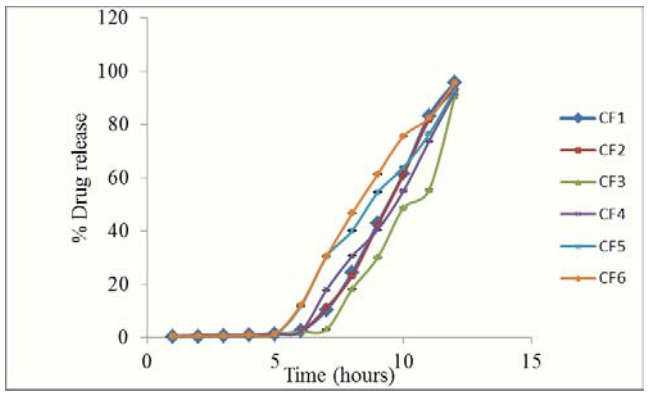


Figure 5: Drug Release Profile of Coated Formulations F1 to F6.

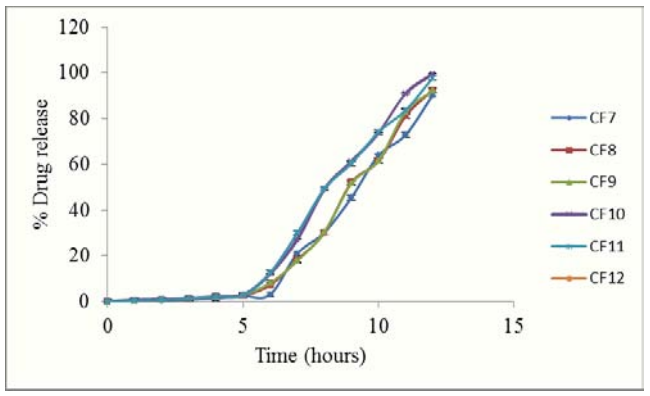


Figure 6: Drug Release Profile of Coated Formulations F7 to F12.

Table 8: Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.01±0.62	0.55±0.27	0.645±0.13	14.72±0.62	0.85
F2	34.87±0.06	0.57±0.18	0.66±0.09	13.63±0.12	0.86
F3	32.74±0.12	0.53±0.22	0.606±0.04	14.19±0.26	0.858
F4	35.33±0.62	0.531±0.31	0.613±0.03	13.37±0.38	0.866
F5	36.24±0.05	0.549±0.14	0.641±0.17	14.35±0.54	0.856
F6	36.12±0.45	0.564±0.32	0.666±0.11	15.31±0.22	0.846

Evaluation of Misoprostol Core Tablets

Misoprostol powder was compressed directly into a core tablet by using direct compression vehicle such as magnesium stearate and talc. The hardness of the core tablets of Misoprostol was found to be in the range of 8.4 ± 0.1 to 9.4 ± 0.21 kg/cm. The core tablets of Misoprostol were also found to comply with the friability tests in the weight loss was found to be in the range of 0.25 ± 0.032 to 0.55 ± 0.021 %.The tablets thickness was found to be in the range of 2.81 ± 0.022 to 2.96 ± 0.043 mm.All formulations were complying with the Indian Pharmacopoeia specifications. Thus the core tablets of Misoprostol formulated in the study were found to have the required characteristics for compression coating with Eudragit L100 and Eudragit S100.

Quality Control Parameters for Core and Coatedformulation Table 9 and Table 10

Evaluation of Misoprostol Coated Tablets: Quality control tests of tablets such as Weight variation (500.51±0.16), Thickness (3.78 ± 0.062), Hardness (6.96 ± 0.20), Friability (0.26 ± 0.015), Drug content (99.54 ±0.27) were performed to spray coated Misoprostol tablets and the results were found to be within the Indian pharmacopoeia specifications. Resulted tablets were evaluated for drug release by using USP dissolution apparatus 2. Assay of tablet shown that tablets are of required purity and matches with Indian pharmacopoeial specification.

In-Vitro Drug Release Studies of Misoprostol of Coated

Table 9: Quality control parameters for (core and coated tablets)

Formulation codes	Weight variation(mg)		Hardness(kg/cm2)	
	Before coating	After coating	Before coating	After coating
CF1	400.7±0.77	501.34±0.56	8.5±0.1	6.8±1.08
CF2	399.91±0.53	500.85±0.25	8.76±0.11	6.73±0.15
CF3	400.34±0.56	508.11±0.69	8.23±0.15	7.26±0.17
CF4	386.59±0.72	507.63±.43	8.4±0.1	6.76±0.11
CF5	400.98±0.57	499.12±0.67	8.8±0.12	7.43±0.05
CF6	398.11±0.12	506±0.01	9.2±0.11	7.76±0.11
CF7	400.55±1.10	500.56±0.52	9.4±0.21	7.68±0.15
CF8	401.34±0.32	502.67±0.03	8.4±0.1	6.4±0.13
CF9	400.58±0.52	500.56±0.77	8.6±0.3	7.46±0.11
CF10	399.02±0.67	500.51±0.16	8.83±0.115	6.96±0.20
CF11	400.56±0.78	502.91±0.68	9.1±0.1	7.63±0.25
CF12	402.91±0.86	501.22±0.14	9.16±0.11	7.26±0.20

Table 10: Quality control parameters for (core and coated tablets)

Formulation codes	Thickness before coating (mm)	Thickness after coating (mm)	Friability before coating (%loss)	Friability after coating (%loss)	Drug content (%)
CF1	2.82±0.014	3.69±0.019	0.36±0.013	0.48±0.011	99.12±0.69
CF2	2.83±0.013	3.66±0.017	0.31±0.011	0.35±0.015	99.26±1.03
CF3	2.85±0.016	3.61±0.033	0.55±0.021	0.34±0.015	99.51±0.59
CF4	2.89±0.041	3.79±0.013	0.34±0.014	0.27±0.015	98.26±1.02
CF5	2.87±0.011	3.77±0.027	0.29±0.020	0.36±0.020	99.51±0.69
CF6	2.81±0.022	3.65±0.036	0.43±0.011	0.25±0.030	99.02±0.59
CF7	2.86±0.028	3.62±0.025	0.25±0.032	0.32±0.045	99.52±1.88
CF8	2.91±0.029	3.73±0.030	0.34±0.029	0.38±0.010	99.09±0.49
CF9	2.87±0.038	3.69±0.045	0.38±0.016	0.23±0.020	98.46±0.67
CF10	2.96±0.043	3.78±0.062	0.41±0.013	0.26±0.015	99.54±0.27
CF11	2.89±0.011	3.81±0.011	0.37±0.019	0.33±0.011	98.13±0.41
CF12	2.88±0.036	3.63±0.028	0.32±0.021	0.25±0.035	99.08±0.52

Tablets

The coated tablets containing 500mg of Misoprostol were tested in Simulated Gastric Fluid (pH1.2), Simulated Intestinal Fluid (pH7.4) and for their dissolution rates. Dissolution studies were performed using USP dissolution test apparatus 2, with 50rpm, at 37±0.5°C. At various time intervals, a sample of 5ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at 275nm and 270nm respectively.

In- vitro drug release studies were conducted to the spray coated Misoprostol tablets and drug release studies shown that formulation F10 have shown good release behavior in colon (99.54 ± 0.20) in 12 hour with limited drug release in stomach and intestine. This indicates that Eudragit L 100 and Eudragit S100 (1:1) in 7.5 % concentration were able to release maximum drug in the colon at 12 hour .This study confirms that Eudragit L 100, Eudragit S 100 act as carrier by using ethyl cellulose as binder to deliver drug to the colon effectively Table 11 and Table 12.

Conclusion

Eudragit L 100 and Eudragit S 100 (1: 1) in combination (7.5 %), in the form of spray coating polymers were capable of protecting Misoprostol from being released in the upper region of Gastro Intestinal system, i.e. Stomach and small intestine. The in-vitro drug release studies indicated that formulation CF10 was a promising system to provide targeting of Misoprostol to the colon. There lease pattern of the above formulation was best fitted to Korsmeyer-Peppas model and zero-order model. Mechanism of drug release followed was non-fickian (super case-II) transport mechanism. FT-IR spectrum studies showed that there was no interaction between the drug and excipients. It was concluded that the release lag time and release rate were able to be tailored through adjusting the formulation variable is to achieve Colon Targeting Drug Delivery of Misoprostol.

Table 11: *In- vitro* Drug Release profile for coated formulations (F1- F6)

Time(hrs)	CF1	CF2	CF3	CF4	CF5	CF6
1	0.26±0.23	0.42±0.24	0.34±0.24	0.73±0.28	0.51±0.11	0.52±0.18
2	0.43±0.26	0.54±0.21	0.54±0.33	0.98±0.22	0.64±0.19	0.57±0.29
3	0.71±0.29	0.65±0.27	0.65±0.26	1.11±0.17	0.86±0.24	0.68±0.33
4	0.93±0.37	0.87±0.1	0.89±0.18	1.28±0.31	1.11±0.35	0.95±0.20
5	1.38±0.35	1.18±0.23	1.26±0.32	1.52±0.17	1.29±0.16	1.44±0.12
6	2.56±0.33	2.45±0.16	2.22±0.17	2.39±0.27	11.71±0.21	12.30±0.23
7	10.35±0.31	11.28±0.20	3.05±0.21	17.880.22	30.22±0.15	30.44±0.24
8	24.26±0.20	23.04±0.30	18.41±0.13	30.45±0.15	40.18±0.22	46.61±0.19
9	42.92±0.17	42.24±0.14	30.05±0.34	40.59±0.16	54.53±0.21	61.30±0.22
10	61.50±0.26	61.13±0.30	48.69±0.31	55.01±0.30	63.88±0.16	75.68±0.17
11	83.29±0.19	81.79±0.20	55.38±0.22	73.85±0.19	76.53±0.19	82.53±0.25
12	95.72±0.25	93.39±0.12	90.69±0.26	91.92±0.19	93.06±0.26	95.72±S0.32

Table 12: *In-vitro* Drug Release profile for coated formulations (F7-F12)

Time(hrs)	CF 7	CF 8	CF 9	CF 10	CF 11	CF 12
1	0.26±0.16	0.35±0.29	0.46±0.28	0.74±0.17	0.49±0.31	0.49±0.39
2	0.39±0.22	0.56±0.14	0.59±0.16	0.98±0.28	0.77±0.28	0.69±0.21
3	0.98±0.13	1.21±0.30	1.32±0.22	1.35±0.34	1.24±0.12	1.04±0.42
4	1.44±0.42	2.05±0.21	2.14±0.34	2.15±0.26	2.16±0.22	1.56±0.19
5	2.41±0.19	2.65±0.26	2.90±0.27	2.94±0.20	2.73±0.19	2.27±0.24
6	3.06±0.28	7.22±0.17	8.11±0.19	12.16±0.22	12.57±0.31	12.30±0.15
7	20.94±0.36	18.19±0.13	17.72±0.26	27.26±0.12	29.98±0.24	29.74±0.21
8	30.26±0.17	30.27±0.24	30.40±0.34	49.12±0.31	49.24±0.27	48.74±0.44
9	45.44±0.24	52.06±0.28	51.64±0.21	61.22±0.17	60.33±0.21	59.72±0.17
10	63.86±0.31	61.**40±0**.19	**61.59±0.39**	73.87±0.28	74.16±0.32	72.68±0.32
11	72.93±0.15	81.13±0.22	**82.97±0.27**	90.93±0.43	83.65±0.17	82.99±0.26
12	90.23±0.24	92.45±0.32	92.18±0.43	99.54±0.20	97.74±0.25	93.58±0.19

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