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FORMULATION AND IN VITRO EVALUATION OF ORAL COLON TARGETED TABLET OF PYRANTEL PAMOATE

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ABSTRACT

In the present study it has been aimed at developing pH sensitive tablets of Pyrantel Pamoate for local action in proximal colon, with a view of minimizing the drug release in the physiological environment of stomach and small intestine and to ensure maximum drug release in the physiological environment of proximal colon with an improved patient compliance, least side effects, better drug therapy and all aspects of an ideal drug delivery system. Twenty seven formulations (F1-F27) were prepared by wet granulation method using 3^3 Response surface method where 3^3 indicates 3 variables and 3 levels of natural polymers of different ratio Okra Gum, Tamarindus Indica and Gum Kondagogu (low, middle and high concentrations) by using Design of experiment software. The Preformulation properties were carried out and the values obtained were within the range. And FTIR studies results revealed that there was no incompatibility between drug and excipients. Thus, colon Tablets were formulated by varying proportions of polymers by wet granulation method and they were evaluated. All the physico-chemical properties of the formulations were within the limit. The formulation F26 was selected as optimized formulation because it showed minimum release in stomach and small intestine and a maximize release in proximal colon. In vitro drug release studies were carried out to know the drug release with respective of the time. Maximum drug was released from the formulation F26 within 24 Hrs. Based on the physico-chemical properties and in vitro drug release, the formulation F26 was concluded as the best formulation. No prominent changes in physico-chemical properties of formulation after its exposure to accelerated conditions of temperature (40 ± 2^0C) and humidity conditions (75 ± 5%RH) were seen. Hence the developed formulation was found to be stable even after subjecting to accelerated stability conditions.

KEY WORDS

Pyrantel Pamoate, Okra Gum, Tamarindus Indica and Gum Kondagogu

INTRODUCTION

Site-specific delivery of drugs to the site of action has the potential to reduce side effects and to increase pharmacological response. One of the seemingly interesting areas to target drugs through oral route is the colon. Various systems have been developed for colon-specific drug delivery: covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time-dependent release systems, and enzymatically controlled delivery systems. pH sensitive polymer coated systems are most commonly used for colonic drug delivery. The drawback of the time-dependent release system is its inability to sense any variation in the upper gastrointestinal tract transit time; besides, any variation in gastric emptying time may lead to drug release in the small intestine before arrival to the colon. To overcome this drawback of premature release of drug from dosage form into stomach and small intestine

eudragit L100 coated tablet was prepared because eudragit L100 degrade only above pH 7 and thus premature release is avoided due to coating [1, 2].

Drug delivery to the colon is beneficial not only for the oral delivery of proteins and peptide drugs (degraded by digestive enzymes of stomach and small intestine) but also for the delivery of low molecular weight compounds used to treat diseases associated with the colon or large intestine such as ulcerative colitis, diarrhoea, and colon cancer. In addition, the colon has a long retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs [3]. The colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease [4]. Colon delivery of a therapeutic drug may reduce the systemic side effects and provide effective and safe therapy that may reduce the dose and duration of therapy when compared with the conventional treatment. However, various strategies have been used for targeting colon, such as pH-sensitive polymers, coating with biodegradable polymers, fabrication of pro-drugs, timed release systems, embedding in biodegradable matrices and hydrogels [5, 6]

The release of drug load in colon region is depended on pH of GIT, gastro intestinal transit time and microbial flora and their enzymes to degrade coated polymers and breaking bonds between carrier molecule and drug molecule. The preferred CTDDS is that should release maximum drug load in colon region. Among different approaches the pH dependent system is less suitable than others due to the large inter and intra subject variation in the gastro intestinal pH, but gives better results with combination of time-dependent system, microbially activated system and others.

Pyrantel Pamoate binds selectively and with high affinity to glutamate-gated chloride ion channels in invertebrate muscle and nerve cells of the microfilaria. This binding causes an increase in the permeability of the cell membrane to chloride ions and results in hyperpolarization of the cell, leading to paralysis and death of the parasite. Pyrantel Pamoate also believed to act as an agonist of the neurotransmitter gamma-aminobutyric acid (GABA), thereby disrupting GABA-mediated central nervous system (CNS) neurosynaptic transmission. Pyrantel Pamoate may also impair normal intrauterine development of O. volvulus microfilariae and may inhibit their release from the uteri of gravid female worms. To eradicate these side effects, the release of Pyrantel Pamoate in the stomach and intestine must be minimized which in turn can be achieved by targeting Pyrantel Pamoate to its primary site of action i.e. proximal colon. Hence, the present work deals with the preparation and evaluation of colon targeted delivery systems containing Pyrantel Pamoate.

MATERIALS AND METHODOLOGY

The drug Pyrantel Pamoate was obtained as gift sample and used as supplied by hetero drugs Hyderabad. All other polymers and chemicals obtained were used as supplied by the standard manufacturers.

Preparation of colon tablets of Pyrantel Pamoate [7]

Twenty-seven formulations (F1-F27) were prepared by wet granulation method using 3^3 Response surface method (3 variables and 3 levels of polymers) by using Design of experiment software with natural polymers like Okra Gum, Tamarindus Indica and Gum Kondagogu. All the formulations were varied in concentration of Polymers and diluent constituted in all the formulations. All the ingredients were passed through sieve no 85# and were mixed uniformly. Granulation was carried out with sufficient quantity of binder solution (PVP K 30 - 5% in Isopropyl alcohol). The wet mass was passed through sieve no 12# and dried at 45^0C for 2 hr. Dried granules were sized by sieve no.18# and add magnesium stearate and talc. Granules obtained were compressed with 8 mm flat punch (Cadmach, Ahmedabad, India). Formulation trials of colon matrix tablets of Pyrantel Pamoate given in Table No:1.

pH sensitive coating of prepared compression tablets [8]

Compression tablets of Pyrantel Pamoate were further coated with pH sensitive coating polymers by dip coating method. Required quantity of Eudragit L 100 was dissolved in acetone using a magnetic stirrer. After complete solubilization of polymer, castor oil (10% w/w of dry polymer) was added as plasticizer. Talc (0.1% w/v) was added as antiadherant and the solution was stirred for 15 min. Pre-weighted compression tablets were dipped for 3-5 times into the solution until 10% weight gain. Composition of coating solution given in Table no: 2.

Table no 1: Formulation trials of colon matrix tablets of Pyrantel Pamoate

F.NO	Pyrantel Pamoate	Okra Gum	Tamarindus Indica	Kongagogu Gum	PVP K-30	DCP	Mg Stearate	TOTAL
F1	180	30	30	15	6	36	3	**300**
F2	180	10	25	10	6	66	3	**300**
F3	180	10	20	15	6	65	3	**300**
F4	180	30	25	10	6	45	3	**300**
F5	180	20	20	20	6	51	3	**300**
F6	180	30	20	15	6	46	3	**300**
F7	180	10	30	10	6	61	3	**300**
F8	180	20	30	10	6	51	3	**300**
F9	180	20	20	15	6	56	3	**300**
F10	180	20	30	15	6	46	3	**300**
F11	180	30	20	20	6	41	3	**300**
F12	180	30	20	10	6	51	3	**300**
F13	180	20	25	15	6	51	3	**300**
F14	180	10	25	15	6	61	3	**300**
F15	180	10	30	15	6	56	3	**300**
F16	180	10	20	20	6	61	3	**300**
F17	180	10	20	10	6	61	3	**300**
F18	180	30	30	10	6	41	3	**300**
F19	180	20	25	20	6	46	3	**300**
F20	180	10	25	20	6	56	3	**300**
F21	180	20	25	10	6	56	3	**300**
F22	180	30	30	20	6	31	3	**300**
F23	180	30	25	15	6	41	3	**300**
F24	180	30	25	20	6	36	3	**300**
F25	180	10	30	20	6	51	3	**300**
F26	180	20	20	10	6	61	3	**300**
F27	180	20	30	20	6	41	3	**300**

Table no 2: Composition of coating solution

S. No	Composition	Quantity
1	Eudragit L 100	10% w/v
2	Acetone	95 ml
3	Water	5 ml
4	Castor oil	0.1% w/v
5	Talc	0.1% w/v
	Total weight gain	+ 10% w/v

EVALUATION TESTS

Pre-compression evaluation tests [9,10,11] Angle of repose, bulk density, tapped density, compressibility index (carr's index), hausner's ratio were performed

Post compression evaluation tests

Weight variations, Thicknesses, Hardness, Friability, and Content Uniformity were performed

***In Vitro* Drug Dissolution Study**

The dissolution of prepared colon tablet formulations was carried out by obeying below conditions mentioned in Table No 3.

Table no 3: specification condition for dissolution studies

Dissolution Apparatus	USP Dissolution Apparatus Type II (Paddle)
Dissolution Medium	0.1N HCL (pH 1.2), Phosphate buffer (pH 6.8), Phosphate buffer (pH 7.4)
Dissolution Medium Volume	900 ml
Temperature	37±0.2 °C
Aliquot Volume	5ml
Replishing Volume	5ml
Speed	100 rpm
Estimation	284nm in UV Spectrophotometer
Time Intervals (Hours)	1,2,4,6,7,8,10,12

Kinetic Model Fitting [12, 13] Over the recent years, the *in vitro* dissolution has been recognized as an important tool in drug development. *In vitro* dissolution has been recognized as an important parameter in quality control and under certain conditions, it can be used as a surrogate for the assessment of bio-equivalence or prediction of Bioequivalence. Guidance recommends USP dissolution apparatus 1, 2, 3 or 4 for modified release dosage forms and generally this equipment is satisfactory. However, modifications of current dissolution equipment or completely new agitation, changing the media, and holding the dosage form in the media without interfering with the release mechanism require careful planning.

An appropriate drug release test is required to characterize the drug product and ensure batch to batch reproducibility and consistent pharmacological/biological activity and to evaluate scale up and post approval changes such as manufacturing site changes, component and composition changes. The release of drug from a sustained release formulation is controlled by various factors through different mechanism such as diffusion, erosion or osmosis. Several mathematical models are proposed by many researchers to describe the drug release profiles from various systems. In order to characterize the kinetics of drug release from dosage forms several model dependent methods are reported by various researchers.

The model dependent methods all rely upon a curve fitting procedure. Different mathematical functions have been used to model the observed data. Both the linear and non-linear models are being used in practice for dissolution modeling. Linear models include Zero order, Higuchi, Hixon – Crowell, Quadratic and Polynomials, whereas the nonlinear models include Weibull, KorsMeyer – Peppas, Logistic etc.

There are several linear and non-linear kinetic models to describe release mechanisms and to compare test and Reference dissolution profiles are as follows:

- **Zero order kinetics**
- **First order kinetics**
- **Higuchi**
- **Korsmeyer-Peppas model**

Drug-excipient compatibility studies [14]

While development of new drug delivery systems the drug will be influenced a lot by excipients and solvents used and may lead to degradation of drug so, the stability and purity of the drug (Pyrantel Pamoate) in presence of other excipients before formulation were determined by various techniques like Infrared Spectroscopy (IR) with which future complications can be investigated and predicted.

FTIR spectra of Pure Drug sample and its physical mixture along with formulation additives of colon tablets and Optimized formulation were testaments with FTIR instrument.

Stability studies [15] Among all tablets compressed of distinct batches, optimized formulation F26 was subjected to stability studies in accordance with guidelines of ICH stability protocol. The test specifications include Temperature of 40 ^{0}C ± 2 ^{0}C and relative humidity of 75±5% RH for a time period of 6 months in Humidity chamber (REMI, Mumbai). The specifications to be evaluated in stability study period include Content Uniformity, Hardness and *in vitro* drug release.

RESULTS AND DISCUSSION FOR PYRANTEL PAMOATE

The standard calibration curve of pyrantel pamoate was developed in different pH media such as 0.1N HCl, pH 6.8 and pH 7.4 phosphate buffer. Standard graph of pyrantel pamoate in 0.1N HCl, pH 6.8 and pH 7.4 phosphate buffer shows linearity with correlation coefficient of 0.9969, 0.9993 and 0.9892. Figure1, Figure

2 and Figure 3 shows the standard graph data in 0.1N HCl, pH 6.8 and pH 7.4 phosphate buffers respectively.

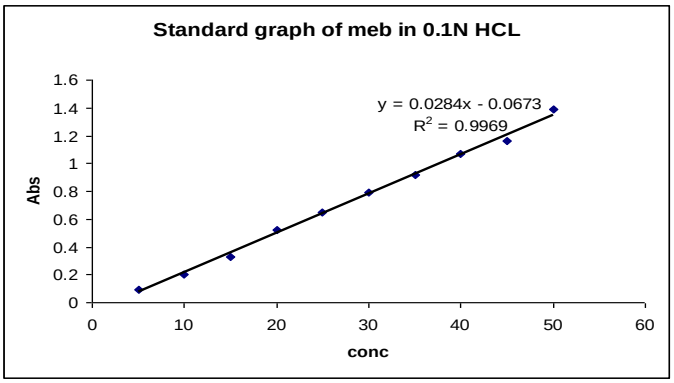

Figure No 1: Standard calibration graph of Pyrantel Pamoate in 0.1N HCl

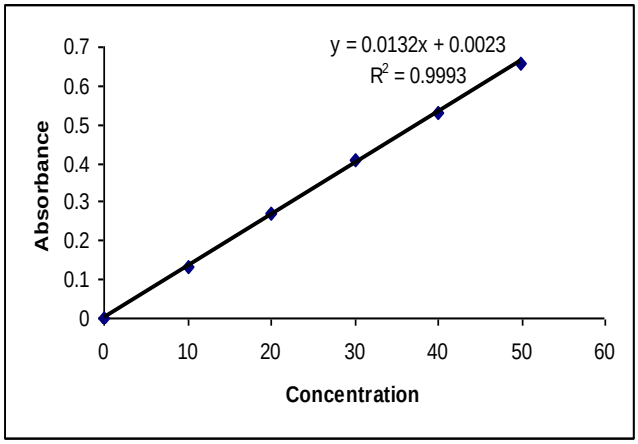

Figure No 2: Standard Calibration curve of pyrantel pamoate in phosphate buffer pH 6.8

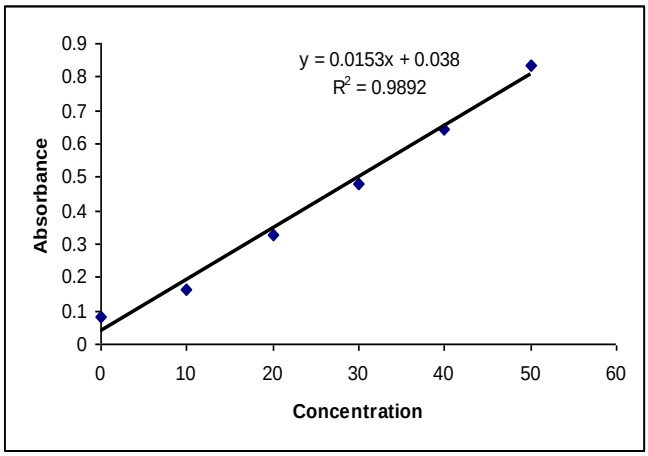

Figure No 3: Standard Calibration curve of pyrantel pamoate in phosphate buffer pH 7.4

FTIR Spectrum:

FTIR study on the pure drug and selected formulation F26 was done. The spectrum peak points of the formulation F26 were similar with that of the pure pyrantel pamoate, clearly indicating that there is no drug polymer interaction. The FTIR spectra of pure pyrantel pamoate and formulation F26 were given in the following section (Figure 4 & 5 and data in table no 4&5)

Table No 4: FTIR interpretation of Pyrantel Pamoate

S. No	Functional Group present	Type of Vibrations	Reference Peak (cm^{-1})	Observed Peak (cm^{-1})
1	Alcohols	O-H Stretch	3000-2500	2993
2	Aromatic	Ar-H Stretch	3050-3000	3026
3	Ester	C=O Stretch	1750-1735	1741.44
4	Aliphatic	C-H Stretch	2960-2850	2866
5	Aromatic	C=C Stretch	1600-1700	1650.23
6	Ether	C-O Stretch	1150-1070	1162.74

Table No 5: FTIR interpretation of Pyrantel Pamoate optimized formulation F26

S. No	Functional Group present	Type of Vibrations	Reference Peak (cm^{-1})	Observed Peak (cm^{-1})
1	Alcohols	O-H Stretch	3000-2500	2871
2	Aromatic	Ar-H Stretch	3050-3000	3032
3	Ester	C=O Stretch	1750-1735	1743
4	Aliphatic	C-H Stretch	2960-2850	2871
5	Aromatic	C=C Stretch	1600-1700	1656
6	Ether	C-O Stretch	1150-1070	1161

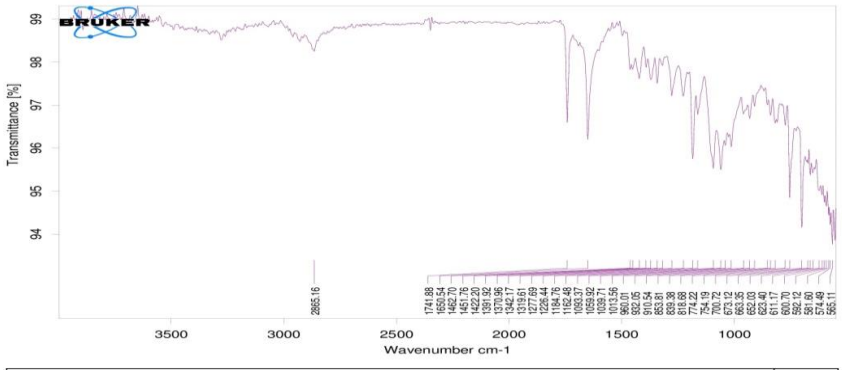

Figure No 4: FTIR Spectrum of pure Pyrantel Pamoate

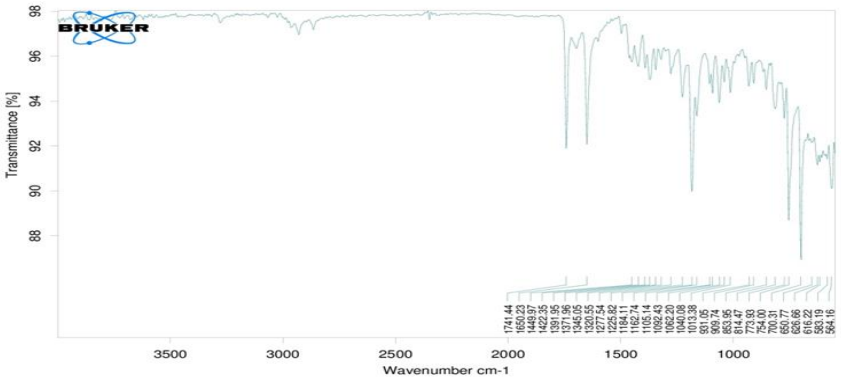

Figure No 5: FTIR Spectrum Pyrantel Pamoate optimized formulation

Physical parameters of prepared powder blends of colon DDS

The results of bulk densities of formulations bearing F1 to F27 reported being in the range of 0.50g/cc to 0.65g/cc.

The findings of tapped density formulations F1 to F27 reported being in the range of 0.57g/cc to 0.69g/cc.

The angle of repose of all the formulations was Found with a satisfactory result. The formulation F26 was found to be (Ɵ=22.12) having good flow property.

The compressibility index values were found to be in the range of 8 to 12 %. These findings indicated that the all the batches of formulations exhibited good flow properties.

The Hausner's ratio values in the space of 1.10 to 1.16 %. These findings designated that all the batches of formulations advertised good flow criterions. Physical properties of prepared powder blends of colon core tablet are mentioned in Table No:6

Physico-chemical properties of Pyrantel Pamoate colon tablets

The prepared tablets were evaluated for different physicochemical properties and the results are found to be within the pharmacopoeial limits, which depicted in Table no7 and 8 (core and coated tablets)

The Weight variation of all formulations witnessed to be in the limit allowed that is ± 5% of total tablet weight.

The suitable hardness for compressed tablets is considered as a vital function for the end user. The deliberated crushing strength of fabricated tablets of formulations F1-F27 trended between 5.0-6.0kg/cm^2 and the thickness of all the formulations between the ranges 3.0-3.5 mm. The friability of all prepared formulation between 0.52-0.89.the friability properties limits are in between 0-1%.

The drug content of all formulation is in between 94.11-99.78%, drug content depends on the angle of repose since the angle of repose indicates uniform flow nature of powder blend which makes the drug to evenly distribute in all the formulation and to maintain content uniformity in all batches.

The Swelling study of colon Pyrantel Pamoate tablets was given in Table no:7

Table No 6: Physical properties of prepared powder blends of colon core tablet

Formulation	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose(Θ)	Carr's index (%)	Hausner ratio
F1	0.56±0.02	0.57±0.01	24.34±0.4	09.23±0.8	1.13±0.02
F2	0.53±0.12	0.58±0.04	21.67±0.3	08.23±1.0	1.11±0.07
F3	0.59±0.04	0.64±0.05	26.54±0.1	10.12±0.7	1.13±0.09
F4	0.50±0.04	0.68±0.04	23.89±0.2	11.34±0.6	1.14±0.03
F5	0.65±0.02	0.69±0.02	22.56±0.1	11.23±0.8	1.11±0.05
F6	0.50±0.21	0.66±0.12	23.30±0.1	10.23±0.5	1.12±0.06
F7	0.52±0.06	0.64±0.03	25.56±0.2	10.34±1.0	1.14±0.06
F8	0.53±0.01	0.68±0.03	24.67±0.3	09.11±0.8	1.12±0.03
F9	0.57±0.01	0.61±0.01	25.56±0.3	09.45±0.7	1.13±0.02
F10	0.58±0.13	0.67±0.06	21.66±0.2	11.45±0.5	1.15±0.01
F11	0.53±0.09	0.68±0.12	25.34±0.2	10.23±0.5	1.13±0.01
F12	0.57±0.06	0.64±0.21	22.99±0.5	11.34±0.5	1.12±0.01
F13	0.54±0.01	0.67±0.04	25.14±0.3	09.67±0.4	1.11±0.02
F14	0.51±0.04	0.66±0.07	24.09±0.2	10.23±0.4	1.14±0.03
F15	0.53±0.01	0.63±0.04	22.78±0.4	10.45±0.3	1.10±0.02
F16	0.54±0.02	0.61±0.07	22.45±0.4	09.68±0.2	1.13±0.02
F17	0.59±0.21	0.68±0.03	25.09±0.3	11.47±0.8	1.12±0.02
F18	0.58±0.03	0.67±0.08	23.05±0.2	11.99±0.3	1.14±0.02
F19	0.56±0.02	0.61±0.12	25.06±0.2	11.45±0.6	1.13±0.01
F20	0.59±0.06	0.64±0.1	24.78±0.1	10.12±0.5	1.15±0.01
F21	0.59±0.07	0.63±0.03	25.34±0.4	11.09±0.4	1.16±0.02
F22	0.56±0.15	0.63±0.04	21.12±0.3	09.34±0.2	1.10±0.03
F23	0.58±0.13	0.66±0.13	24.45±0.3	10.67±0.4	1.14±0.02
F24	0.56±0.12	0.68±0.05	25.56±0.2	09.68±0.6	1.14±0.05
F25	0.56±0.13	0.62±0.06	23.67±0.5	11.24±0.5	1.11±0.05
F26	0.53±0.12	0.65±0.02	22.12±0.3	09.39±0.5	1.13±0.05
F27	0.55±0.09	0.66±0.12	25.56±0.2	11.05±0.7	1.14±0.02

Table No 7: Physico-chemical parameters of Pyrantel Pamoate colon core tablets

F. No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	Swelling index (%)
F1	151.65±1.2	3.0±0.12	5.6±0.12	0.52±0.01	95.23±0.63	73±0.76
F2	148.69±0.8	3.1±0.06	5.1±0.06	0.55±0.02	97.04±0.06	79±0.72
F3	148.04±0.5	3.1±0.06	5.1±0.06	0.63±0.03	95.56±0.14	78±0.64
F4	151.05±0.0	3.2±0.12	5.2±0.12	0.72±0.01	98.11±1.01	88±0.81
F5	151.54±0.4	3.3±0.00	5.4±0.00	0.62±0.02	94.23±0.8	73±1.03
F6	150.78±0.4	3.3±0.10	5.1±0.06	0.66±0.01	95.45±0.31	72±0.84
F7	150.65±0.3	3.1±0.10	5.4±0.10	0.58±0.02	94.11±0.49	70±0.72
F8	149.57±0.2	3.5±0.25	5.3±0.40	0.69±0.01	97.23±0.51	82±0.79
F9	150.76±0.35	3.4±0.06	5.6±0.06	0.58±0.00	96.13±0.56	81±0.80
F10	150.49±0.2	3.2±0.20	5.2±0.42	0.79±0.02	95.23±0.24	77±0.46
F11	151.53±0.4	3.2±0.06	5.6±0.06	0.76±0.01	97.97±0.21	86±0.67
F12	152.58±0.3	3.3±0.00	5.4±0.06	0.73±0.02	97.45±0.76	88±0.93
F13	151.34±0.2	3.5±0.26	5.8±0.35	0.72±0.02	97.45±0.48	96±0.53
F14	148.67±0.3	3.1±0.21	5.4±0.21	0.74±0.03	96.98±0.23	83±1.08
F15	149.65±0.2	3.4±0.06	5.0±0.23	0.75±0.02	96.45±0.36	90±0.91
F16	150.65±0.3	3.2±0.25	5.4±0.23	0.78±0.01	96.45±0.69	88±0.63
F17	151.79±0.4	3.5±0.15	5.8±0.32	0.79±0.01	96.34±0.35	93±0.48
F18	151.87±0.1	3.5±0.25	5.7±0.35	0.82±0.01	97.56±0.23	95±0.90
F19	149.67±0.3	3.6±0.12	6.0±0.12	0.84±0.03	96.29±0.34	90±0.75
F20	149.32±0.2	3.2±0.12	5.5±0.2	0.63±0.03	97.18±0.81	88±0.67
F21	148.27±0.4	3.3±0.06	5.3±0.06	0.66±0.02	96.27±0.11	90±0.54
F22	150.27±0.1	3.4±0.12	5.2±0.12	0.53±0.03	99.18±0.07	98±0.67
F23	150.26±0.13	3.3±0.17	5.8±0.4	0.76±0.05	96.14±0.76	88±0.54
F24	150.10±0.5	3.5±0.00	5.7±0.23	0.73±0.08	97.16±0.12	96±0.86
F25	149.12±0.6	3.1±0.17	5.6±0.12	0.67±0.02	96.23±0.00	93±0.70
F26	150.16±0.8	3.4±0.10	5.7±0.21	0.52±0.89	99.78±0.23	98±0.68
F27	148.29±0.15	3.5±0.29	5.9±0.45	0.89±0.03	97.10±0.40	97±0.75

***Values are expressed in mean± SD :(n=20); #Values are expressed in mean± SD :(n=3)**

Physico-chemical parameters of Pyrantel Pamoate colon coated tablets were mentioned in Table No 8.

Table No 8: Physico-chemical parameters of Pyrantel Pamoate colon coated tablets

F.No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)
F1	166.65±1.2	3.5±0.12	5.9±0.12	0.42±0.01
F2	163.69±0.8	3.6±0.06	6.1±0.06	0.45±0.02
F3	165.04±0.5	3.7±0.06	6.1±0.06	0.43±0.03
F4	167.05±0.0	3.8±0.12	6.2±0.12	0.52±0.01
F5	168.54±0.4	3.8±0.00	6.4±0.00	0.42±0.02
F6	165.78±0.4	3.7±0.10	6.1±0.06	0.46±0.01
F7	166.65±0.3	3.6±0.10	6.4±0.10	0.38±0.02
F8	167.57±0.2	4.2±0.25	6.3±0.40	0.49±0.01
F9	168.76±0.35	3.8±0.06	6.2±0.06	0.38±0.00
F10	169.49±0.2	3.8±0.20	6.2±0.42	0.59±0.02
F11	166.53±0.4	3.8±0.06	6.6±0.06	0.56±0.01
F12	165.58±0.3	3.7±0.00	6.4±0.06	0.53±0.02
F13	166.34±0.2	3.8±0.26	6.8±0.35	0.52±0.02
F14	169.67±0.3	3.7±0.21	6.4±0.21	0.54±0.03
F15	167.65±0.2	3.9±0.06	5.9±0.23	0.55±0.02
F16	166.65±0.3	3.7±0.25	5.8±0.23	0.58±0.01
F17	169.79±0.4	3.8±0.15	6.1±0.32	0.59±0.01
F18	167.87±0.1	3.7±0.25	6.2±0.35	0.52±0.01

F19	165.67±0.3	3.9±0.12	6.2±0.12	0.54±0.03
F20	168.32±0.2	3.7±0.12	5.9±0.2	0.43±0.03
F21	164.27±0.4	4.3±0.06	5.9±0.06	0.46±0.02
F22	166.27±0.1	4.1±0.12	5.8±0.12	0.33±0.03
F23	165.26±0.13	3.8±0.17	6.1±0.4	0.56±0.05
F24	167.10±0.5	3.9±0.00	5.9±0.23	0.53±0.08
F25	168.12±0.6	3.8±0.17	5.9±0.12	0.47±0.02
F26	165.16±0.8	4.1±0.10	6.2±0.21	0.42±0.89
F27	169.29±0.15	3.9±0.29	6.1±0.45	0.59±0.03

In Vitro Drug Dissolution Study

In vitro release profiles of Pyrantel Pamoate were sequentially determined in0.1 N HCL pH 1.2, intestinal fluid pH 6.8 and simulated colonic fluid (SCF) pH 7.4.

The formulation F26 was selected as optimized formulation because it showed a maximize release in proximal colon. *In vitro* Drug Release Profile for colon Pyrantel Pamoate tablets F1-F7 to were given in Figure No 6, F8-F13 In Figure No 7, F14-F20 Figure No 8 & F21-F27 In Figure No 9 and Comparative *In vitro* study plot of optimized formulation (F26) and conventional marketed tablet given on Figure No: 10.

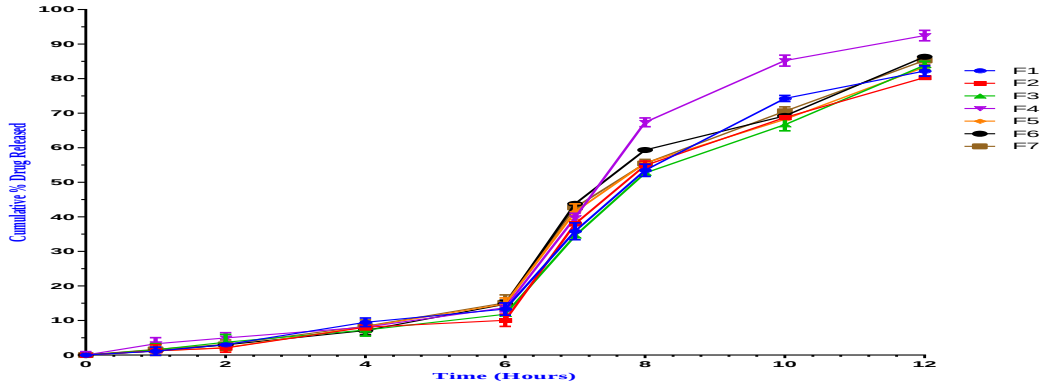

Figure No 6: *In vitro* Drug Release Profile for colon Pyrantel Pamoate tablets F1-F7

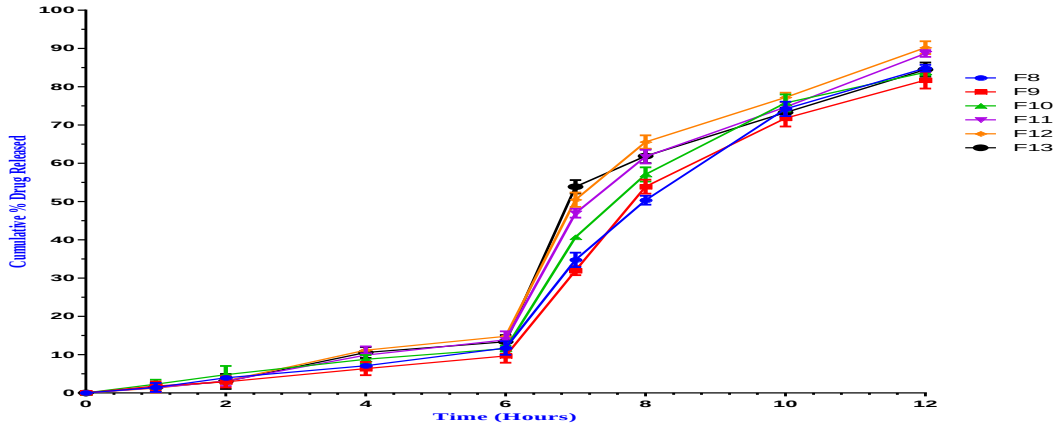

Figure No 7: *In vitro* Drug Release Profile for colon Pyrantel Pamoate tablets F8-F13

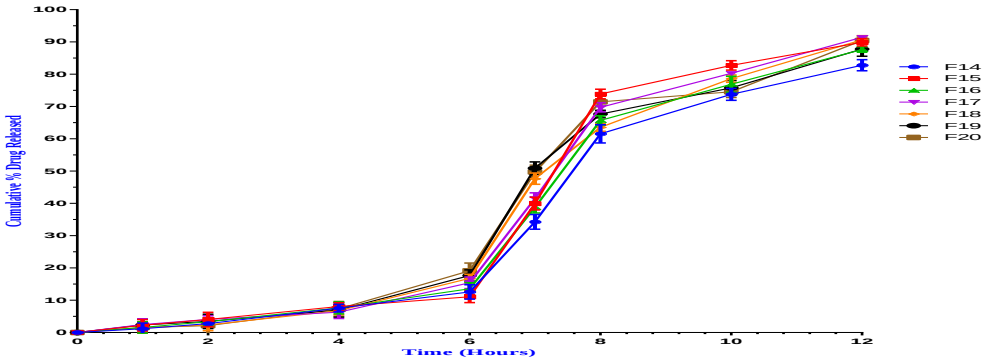

Figure No 8: *In vitro* Drug Release Profile for colon Pyrantel Pamoate tablets F14-F20

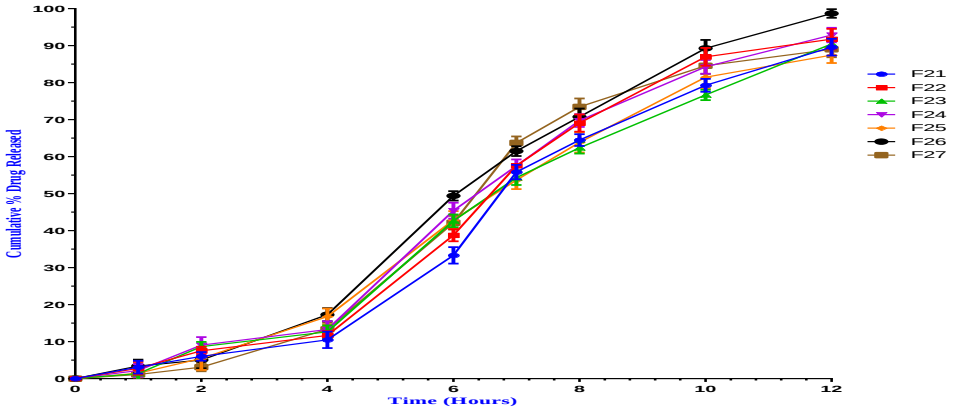

Figure No 9: *In vitro* Drug Release Profile for colon Pyrantel Pamoate tablets F21-F27

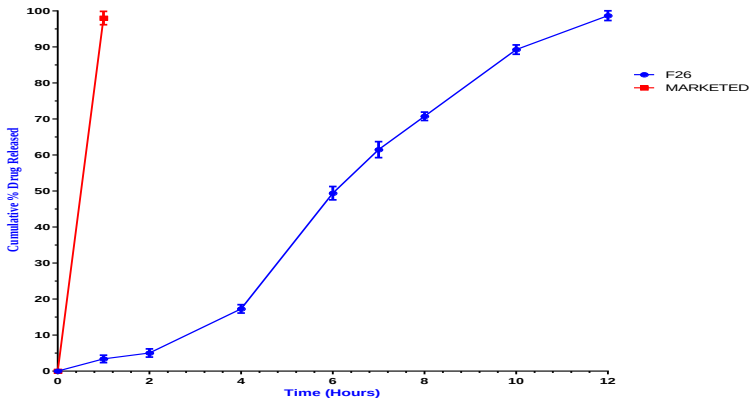

Figure No 10: Comparative *In vitro* study plot of optimized formulation (F26) and conventional marketed tablet

Mathematical modeling of optimized formula (F26) of Pyrantel Pamoate colon tablets

In vitro dissolution has been recognised as an important element in drug development. Under certain conditions it can be used as a surrogate for the assessment of bioequivalence.There are several models to represent the drug dissoluton profiles where ft is a function of time releated to the amout of drug dissolved from the pharmaceutical dosage systems.The quatitative interpretation of the values obtained in the dissolution assay is facilitated by the usage of a generic eqation that mathematically translates the dissolution curve in the function of some parameters releated with the pharmaceutical dosage forms.

A water-soluble drug incorporated in a matrix is mainly released by diffusion, while for a low water- soluble drug the self-erosion of the matrix will be the principal release mechanism. To accomplish these studies the cumulative profiles of dissolved drug are more commonly used in opposition to their differential profiles. Mathematical modeling of the release kinetics of specific classes of controlled-release systems may be

used to predict solute release rates from and solute diffusion behavior through polymers and elucidate the physical mechanisms of solute transport by simply comparing the release data to mathematical models.

In the view of establishment of release mechanism and quantitatively interpreting and translate mathematically the dissolution date being plotted.

From the obtained results (Table No 9) apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.999 indicates that the drug release follows a zero-order mechanism. This data indicates a lesser amount of linearity when plotted by the first order equation. Hence it can be concluded that the major mechanism of drug release follows zero order kinetics.

Table no 9: Release kinetics of optimized formulation of Pyrantel Pamoate colon tablets (F26)

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	n	R^2	n	R^2	n	R^2	n
CF26	0.999	8.741	0.748	0.151	0.937	29.62	0.959	0.825

Further, the translation of the Data of marketed formulation from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots. Further the n value obtained from the Korsmeyer-Peppas plots i.e. 0.825 indicating non Fickian (anomalous) transport (Table No 9) thus it projected that formulation delivered its active ingredient by coupled diffusion and erosion.

From the above results it is apparent that for marketed formulation the regression coefficient value closer to unity in case of First order plot i.e.0.994 indicates that the drug release follows a first order mechanism (Table No 10). This data indicates a lesser amount of linearity when plotted by the zero-order equation. Hence it can be concluded that the major mechanism of drug release follows first order kinetics.

Table no 10: Release kinetics of Marketed Product

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	n	R^2	n	R^2	n	R^2	n
Marketed	0.927	8.642	0.994	0.061	0.954	24.76	0.971	0.833

Further, the translation of the data from the dissolution studies suggested possibility of understanding the mechanism of drug release by configuring the data in to various mathematical modeling such as Higuchi and Korsmeyer-Peppas plots.

Further the n value obtained from the Korsemeyer-Peppas plots i.e. 0.833 indicating non Fickian (anomalous) transport thus it projected that formulation delivered its active ingredient by coupled diffusion and erosion.

Correlation Coefficient Values for Optimized

The *in vitro* drug release profiles were fitted to several kinetic models and release data followed by their R^2 and n values shown in the Table no 11. The optimized formulation was best fitted in Zero Order and Korsmeyer-Peppas. The optimized formulation n value was 0.835 indicating non Fickian (anomalous) transport thus it projected that formulation delivered its active ingredient by coupled diffusion and erosion. The marketed conventional formulation followed the first order kinetics indicating drug release is directly proportional to the concentration of drug.

Table no 11: Regression coefficient (R^2) values, n.

S. No	Formulation	Zero order R^2	First order R^2	Higuchi Model R^2	Korsmeyer-Peppas model R^2	n
1	**F26**	0.999	0.748	0.937	0.959	0.835
2	**Marketed**	0.927	0.983	0.943	0.968	0.833

Stability study

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (F26) to the Accelerated Stability Studies, the results were shown (Table No:12) that there were no major changes in Drug Content, *In Vitro* Drug Release, Swelling Index and Hardness.

Hence the formulation was found to be stable.

Table no 12: Parameters after Accelerated Stability Study of Formulation F26

Parameters	Temperature Maintained at 40 ±2^{0}C ; Relative Humidity (RH) Maintained at 75%±5%RH			
	Initial	After 1 month	After 2 months	After 3 months
Drug Content (%)	99.78±0.14	99.76±0.68	99.73±0.37	99.72±0.22
***In Vitro* Drug Release (%)**	98.68±1.15	98.09±1.53	98.05±1.42	98.02±1.35
Swelling Index	98.0±0.64	98.0±0.56	98.0±0.67	98.0±0.23
Hardness	6.7±0.56	6.7±0.58	6.7±0.15	6.7±0.27

CONCLUSION

The present research work was involved with the development of the colon targeted tablets, which after oral administration were developed to prevent the drug release in stomach and small intestine. It improves the bioavailability of the drug with less time. Different formulations were developed by using natural polymer like Okra Gum, Tamarindus Indica and Gum Kondagogu and coated by dip coating methods. Formulated coated colon targeted tablets and evaluated the required physicochemical parameters like pre-compression and post-compression such as hardness, friability, weight variation, drug content, *In vitro* drug release studies etc. The formulation F26 was selected as optimized formulation because it showed minimum release in stomach and small intestine and a maximize release in proximal colon. In the present work, it can be concluded that the colon Tablets of Pyrantel Pamoate formulations can be an innovative and promising approach for the delivery of Pyrantel Pamoate for the treatment of worm infections.

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