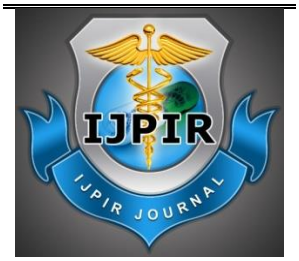
Research Article



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Formulation and evaluation of colon ivermectin immediate release tablets by using natural polymers

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ABSTRACT

In the present study it has been aimed at developing pH sensitive tablets of Ivermectin 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. In present work attempt was made to formulate and evaluate colon tablets of ivermectin. Attempts were made to achieve immediate drug release from the dosage form. Twenty seven formulations (F1-F27) were prepared by direct compression method using 3^3 Response surface method where 3^3 indicates 3 variables and 3 levels of natural superdisintegrants like Gellan Gum, Locust bean Gum and Fenugreek seed Gum (low, middle and high concentrations) by using Design of experiment software. In the Preformulation properties was 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 natural superdisintegrants by direct compression method and all formulations were coated by Eudragit RS 100 coating solution which is a pH sensitive polymer to prevent drug release in stomach and intestine. Entire drug will release in proximal part of colon.

Keywords: Ivermectin, Superdisintegrants, Gellan Gum, Locust bean Gum and Fenugreek seed Gum

INTRODUCTION

The oral route of drug administration is the most convenient and important method of administering drugs for systemic effect. Nearly 50% of the drug delivery systems available in the market are oral D.D.S. and these systems have more advantages due to patient acceptance and ease of administration [1, 2] . During the last decade there has been interest in developing site-specific formulations for targeting drug to the colon. Colonic drug delivery has gained increased importance not just for the delivery of the drugs for the treatment of local diseases associated with the colon like Crohn's disease, ulcerative colitis, irritable bowel syndrome and constipation but also

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for the systemic delivery of proteins, therapeutic peptides, antiasthmatic drugs, antihypertensive drugs and antidiabetic agents [3, 4] . There are various methods or techniques through which colon drug targeting can be achieved, for example, formation of prodrug, coating with pH-sensitive polymers, coating with biodegradable polymers, designing formulations using polysaccharides, timed released systems, pressure controlled drug delivery systems, osmotic pressure controlled systems [5, 6] . Coating of the drugs with pH sensitive polymers provides simple approach for colon specific drug delivery.

In the present study it has been aimed at developing pH sensitive tablets of Ivermectin 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.

MATERIALS AND METHODS

Estimation of Ivermectin [7, 8, 9]

The following methods are available for the estimation of Ivermectin.

Spectrophotometric method

The predetermined maxima wavelength i.e., 254 nm in 0.1N HCl, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 was adopted in the assessment of Ivermectin in dissolution and assay techniques.

Standard solution

100 mg of Ivermectin was dissolved in solvents like 0.1N HCl, Phosphate buffer pH 6.8 and Phosphate buffer pH 7.4 in100mL volumetric flasks separately and the solution was made up to volume with rest solvent.

Preparation of colon tablets of Ivermectin

Twenty seven formulations (F1-F27) were prepared by direct compression method using 3^3 Response surface method (3 variables and 3 levels of polymers) by using Design of experiment software with natural superdisintegrants like Gellan Gum, Locust bean Gum and Fenugreek seed Gum. All the formulations were varied in concentration of natural superdisintegrants, magnesium stearate constituted in all the formulations. All the ingredients were passed through sieve no 85# and were mixed uniformly. Direct compression was carried out with sufficient quantity of binder (PVP K 30). Tablets were compressed with 6 mm flat punch (Cadmach, Ahmedabad, India) [10].

pH sensitive coating of prepared compression tablets

Compression tablets of ivermectin were further coated with pH sensitive coating polymers by dip coating method. Required quantity of Eudragit RS 100 was dissolved in acetone using a magnetic stirrer. After complete solubilisation 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 [11].

Table 1: Formulation trials of colon tablets of Ivermectin

F.NO	Ivermectin	Gellan Gum	Locust bean gum	Fenugreek seed gum	PVP K-30	Mannitol	Mg Stearate	Talc	TOTAL
F1	9	10	8	6	4	59	2	**2**	**100**
F2	9	12	8	6	4	57	2	**2**	**100**
F3	9	14	8	6	4	55	2	**2**	**100**
F4	9	10	10	6	4	57	2	2	**100**
F5	9	12	10	6	4	55	2	**2**	**100**
F6	9	14	10	6	4	53	2	**2**	**100**
F7	9	10	12	6	4	55	2	**2**	**100**
F8	9	12	12	6	4	53	2	**2**	**100**

F9	9	14	12	6	4	51	2	**2**	**100**
F10	9	10	8	8	4	57	2	**2**	**100**
F11	9	12	8	8	4	55	2	**2**	**100**
F12	9	14	8	8	4	53	2	**2**	**100**
F13	9	10	10	8	4	53	2	**2**	**100**
F14	9	12	10	8	4	53	2	**2**	**100**
F15	9	14	10	8	4	51	2	**2**	**100**
F16	9	10	12	8	4	53	2	**2**	**100**
F17	9	12	12	8	4	51	2	**2**	**100**
F18	9	14	12	8	4	51	2	**2**	**100**
F19	9	10	8	10	4	55	2	**2**	**100**
F20	9	12	8	10	4	53	2	**2**	**100**
F21	9	14	8	10	4	51	2	**2**	**100**
F22	9	10	10	10	4	53	2	**2**	**100**
F23	9	12	10	10	4	51	2	**2**	**100**
F24	9	14	10	10	4	49	2	**2**	**100**
F25	9	10	12	10	4	51	2	**2**	**100**
F26	9	12	12	10	4	49	2	**2**	**100**
F27	9	14	12	10	4	47	2	**2**	**100**

Table 2: Composition of coating solution

S. No	Composition	Quantity
1	Eudragit RS 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 [12, 13, 14]

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 disintegration time

The USP device to rest disintegration was six glass tubes that are "3 long, open at the top, and held against 10" screen at the bottom end of the basket rack assembly. One tablet is placed in each tube and the basket rack is poisoned in 1 liter beaker of buffer at 37± 2 ^{0}C, such that the tablets remain below the surface of the liquid on their upward movement and descend not closer than 2.5cm from the bottom of the beaker.

In Vitro Drug Dissolution Study

The dissolution of prepared colon tablet formulations was carried out by obeying below conditions; Dissolution Apparatus USP Dissolution Apparatus Type II (Paddle), Dissolution Medium 0.1N HCL pH 1.2Phosphate buffer pH 6.8 Phosphate buffer (pH 7.4), Dissolution Medium Volume was 900ml, Temperature was 37±0.2°C, Estimation was 254 in UV Spectrophotometer, Time Intervals (Hours) 12,3,4,5,6 & 7

Kinetic Model Fitting [15, 16, 17]

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

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 (Ivermectin) 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. [18]

Compatibility check by FTIR Studies

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.

Table 3: Kinetic Model Fitting

Release exponent (n)	Drug transport mechanism	Rate as a function of time
0.5	Fickian diffusion	$t^{-0.5}$
0.5<n<1.0	Anomalous transport	t^{n-1}
1.0	Case-II transport	Zero-order release
Higher than 1.0	Super Case-II transport	t^{n-1}

This type of analysis of release behavior is valuable is to the formulator for comparative purposes. The Release exponent can be obtained from the slope and the Constant (K_k) obtained from the intercept of the graphical relation between logarithmic versions of left side of the equation versus log t.

Stability studies

Among all tablets compressed of distinct batches, mucoadhesive tablets were subjected to immutability 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 [19]

RESULTS AND DISCUSSION

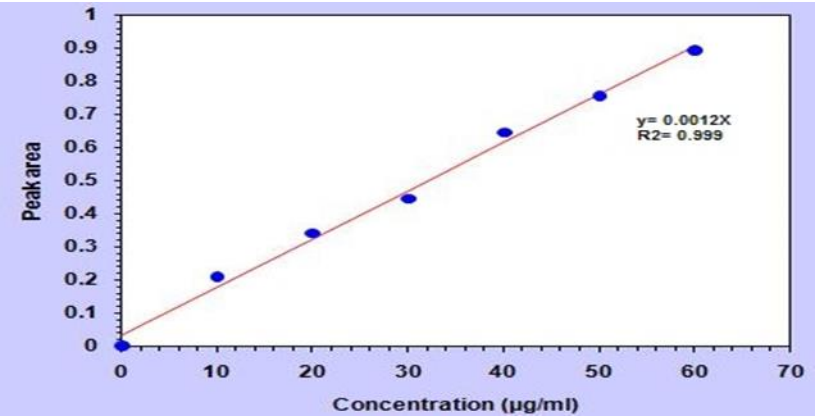

Figure 1: Standard calibration graph of Ivermectin at pH 7.4

FTIR Spectrum of pure ivermectin

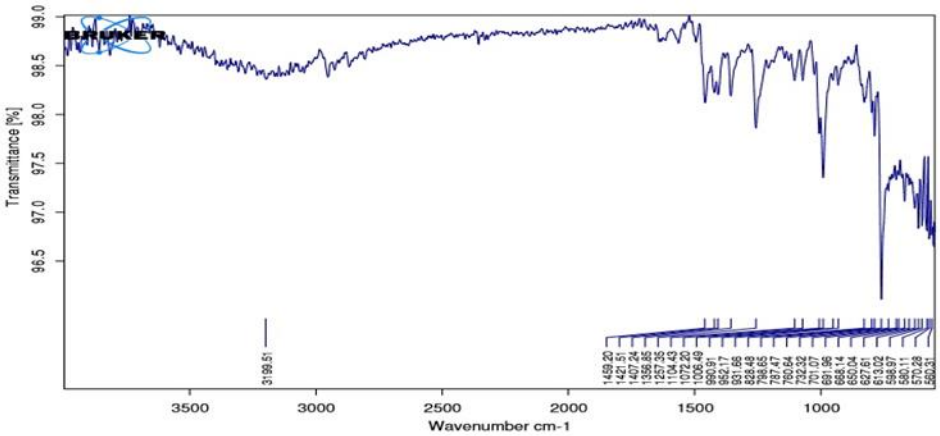

Figure 2: FTIR Spectrum of pure ivermectin

Table 4: FTIR interpretation of ivermectin

Functional groups	Reference peak (cm-1)	Observed peak(cm-1)
Cyclic amines	3200-3500	3250
C-H stretching	3000-2840	2950
O-H bending	1470-1395	1459.20
C-Cl	1000-925	990.91

FTIR Spectrum Ivermectin optimized formulation

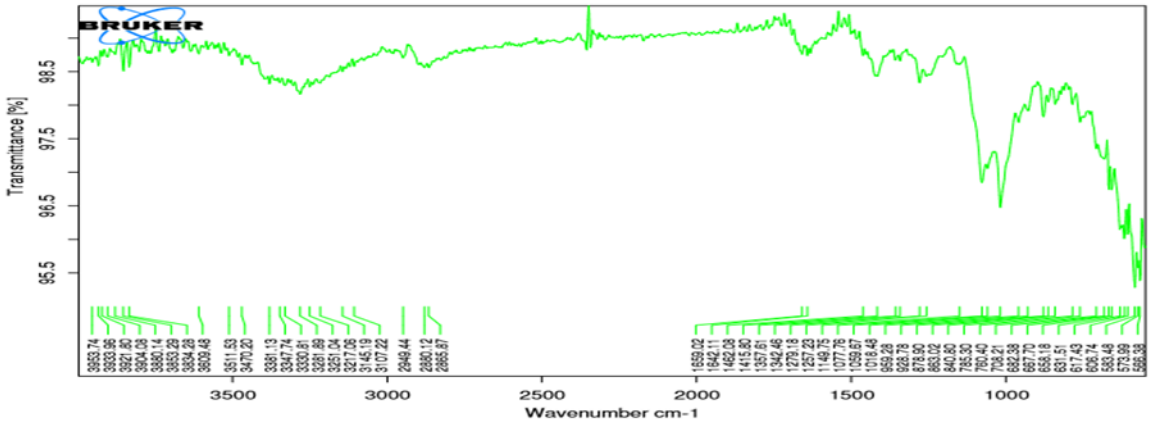

Figure 3: FTIR Spectrum Ivermectin optimized formulation

Table5: FTIR interpretation of ivermectin optimized formulation

Functional groups	Reference peak (cm-1)	Observed peak(cm-1)
Cyclic amines	3200-3500	3281.89
C-H stretching	3000-2840	2949.44
O-H bending	1470-1395	1462.08
C-Cl	1000-925	959.28

Physical parameters of prepared powder blends of colon DDS

Table 6: Physical properties of prepared powder blends of colon tablet

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Angle of repose (θ)	Carr's index (%)	Hausner ratio
F1	0.54±0.19	0.52±0.15	24.34±0.44	09.23±1.12	1.13±0.24
F2	0.57±0.16	0.58±0.17	22.67±0.31	08.23±1.42	1.11±0.10
F3	0.57±0.17	0.64±0.21	26.54±0.41	10.12±0.8	1.13±0.20
F4	0.59±0.25	0.68±0.25	25.89±0.55	11.34±0.6	1.14±0.24
F5	0.57±0.18	0.59±0.18	22.56±0.0.57	12.23±0.12	1.11±0.32
F6	0.58±0.20	0.66±0.20	25.30±0.30	11.23±0.25	1.12±0.30
F7	0.51±0.14	0.64±0.16	22.56±0.57	10.34±0.31	1.14±0.20
F8	0.54±0.16	0.68±0.17	23.67±0.60	09.11±0.24	1.12±0.25
F9	0.65±0.18	0.61±0.19	25.56±0.44	09.45±1.15	1.13±0.70
F10	0.66±0.25	0.67±0.18	21.66±0.31	13.45±1.3	1.15±0.20
F11	0.51±0.17	0.68±0.16	22.34±0.37	14.23±1.5	1.13±0.16
F12	0.55±0.16	0.64±0.20	25.99±0.70	11.34±1.25	1.12±0.12
F13	0.56±0.19	0.66±0.18	23.14±0.50	09.67±1.55	1.09±0.14
F14	0.52±0.13	0.66±0.17	22.09±0.57	10.23±1.55	1.14±0.15
F15	0.51±0.18	0.63±0.16	24.78±0.77	10.45±1.5	1.15±0.15
F16	0.52±0.13	0.61±0.15	23.45±0.80	09.681.3	1.18±0.18
F17	0.58±0.13	0.68±0.19	21.09±0.86	09.47±1.09	1.12±0.15
F18	0.56±0.16	0.67±0.20	23.05±0.75	14.99±1.20	1.14±0.15
F19	0.54±0.18	0.61±0.16	26.06±0.67	12.45±1.45	1.13±0.15
F20	0.58±0.17	0.64±0.17	23.78±0.57	13.12±1.45	1.15±0.17
F21	0.59±0.13	0.63±0.18	25.34±0.70	11.09±1.07	1.16±0.20
F22	0.58±0.15	0.67±0.12	25.12±0.35	14.34±1.06	1.17±0.30
F23	0.55±0.14	0.64±0.21	26.45±0.37	10.67±1.25	1.14±0.35
F24	0.54±0.16	0.64±0.12	25.56±0.31	09.68±1.35	1.14±0.15
F25	0.52±0.19	0.68±0.14	23.67±0.44	13.24±0.24	1.11±0.16
F26	0.51±0.19	0.65±0.16	24.12±0.16	09.39±0.25	1.17±0.18
F27	0.54±0.20	0.64±0.13	22.56±0.43	12.05±0.31	1.18±0.15

Above parameters are communicated as Average ± Standard Deviation; (n=3)

The results of bulk densities formulations bearing F1 to F27 reported being in the range of 0.51g/cc to 0.66g/cc. The findings of tapped density formulations F1 to F27 reported being in the range of 0.52g/cc³ to 0.68g/cc³. The angle of repose of all the formulations was found satisfactory results. The formulation F17 was found to be 21.09 having good flow property.

The compressibility index values were found to be in the range of 8 to 15 %. These findings indicated that the all the batches of formulations exhibited good flow properties.

The Hausner's ratio values in the range of 1.11 to 1.18 %. These findings indicated that the all the batches of formulations exhibited good flow properties.

Physico-chemical properties of ivermectin 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 7

Table 7: Physico-chemical parameters of ivermectin colon core tablets

F.No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)	#Content uniformity (%)	Disintegration tests (Secs)
F1	100.12±0.20	3.1±104	4.1±0.13	0.51±0.08	97.23±1.23	58±0.27
F2	99.23±0.24	3.01.16	4.0±0.33	0.54±0.09	98.04±1.03	77±0.53
F3	98.08±0.15	3.1±1.05	4.3±0.13	0.63±0.07	96.56±0.94	76±0.51
F4	101.09±0.70	3.2±1.09	4.2±0.10	0.56±0.05	98.11±0.63	66±0.93
F5	101.89±0.50	3.1±1.37	4.1±0.10	0.61±0.07	95.23±0.81	55±0.43
F6	100.34±0.20	3.2±1.11	4.2±0.10	0.67±0.09	96.45±0.32	70±1.04
F7	100.23±0.60	3.0±1.61	4.0±0.15	0.54±0.02	95.11±1.17	68±0.64
F8	99.12±0.50	3.2±0.3	4.2±0.15	0.67±0.02	98.23±0.45	50±0.60
F9	100.23±0.48	3.2±0.45	4.2±0.19	0.56±0.02	97.13±1.17	59±0.64
F10	100.24±0.20	3.1±0.25	4.1±0.21	0.77±0.07	96.23±0.49	75±0.65
F11	101.45±0.97	3.1±0.70	4.4±0.10	0.76±0.05	98.97±0.95	44±0.75
F12	02.03±0.54	3.4±0.25	4.6±0.15	0.73±0.08	98.45±0.35	56±0.51
F13	101.04±0.30	3.5±0.60	4.8±0.18	0.52±0.09	99.85±0.24	58±0.78
F14	98.23±0.35	3.1±0.56	4.2±0.10	0.72±0.02	99.18±0.13	81±0.83
F15	99.34±0.25	3.5±0.70	.6±0.08	0.71±0.20	99.25±1.21	89±0.63
F16	101.12±0.55	3.1±0.40	4.2±0.21	0.78±0.9	97.45±1.30	86±0.43
F17	**100.23±0.50**	**3.5±0.17**	**4.7±0.04**	**0.79±0.04**	**99.94±1.31**	**37±0.97**
F18	101.67±0.30	3.5±0.40	4.6±0.14	0.82±0.03	98.56±1.36	44±0.87
F19	99.13±0.45	3.0±0.17	4.0±0.12	0.84±0.01	97.29±1.31	49±1.13
F20	99.45±0.55	3.3±0.96	4.5±0.10	0.63±0.03	97.18±1.36	58±1.23
F21	98.12±0.70	3.2±0.50	4.3±0.12	0.66±0.03	96.27±1.30	50±1.27
F22	101.45±0.80	3.0±0.63	4.0±0.10	0.72±0.015	99.34±1.16	41±0.83
F23	100.23±0.55	3.3±0.78	4.8±0.17	0.76±0.04	99.14±1.46	66±1.21
F24	100.12±0.60	3.4±0.86	4.7±0.14	0.73±0.06	99.16±0.56	51±0.93
F25	99.14±0.75	3.1±0.57	4.6±0.15	0.67±0.07	98.23±0.84	63±0.92
F26	100.18±0.15	3.3±0.63	4.7±0.18	0.72±0.03	98.34±1.16	55±0.18
F27	100.23±0.75	3.6±0.98	4.9±0.05	0.89±0.04	98.10±1.11	63±1.25

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

The Weight variation of all formulations within the limit because weight variation deviation is ± 5 for tablet and weight above 100 mg. The measured hardness of the tablets of each batch of all formulations i.e. F1 to F27 was ranged between 4.0 to 5.0 Kg/cm^2 and the results are shown in Table…. The thickness of the tablets was found to be almost uniform in all formulations F1 to F27. The thickness of all the formulations between the ranges 3.0-3.6 mm.

The friability of all prepared formulation is between 0.53-0.89.the friability properties limits are in between 0-1%. The drug content of all formulation is in between 95.00-99.94%, 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.

Table 8: Physico-chemical parameters of ivermectin colon coated tablets

F.No	*Weight variation (mg)	#Thickness (mm)	#Hardness (Kg/Cm^2)	#Friability (%)
F1	110.12±0.20	3.6±104	4.7±0.13	0.41±0.08
F2	109.23±0.24	3.9.16	4.6±0.33	0.44±0.09
F3	109.08±0.15	3.7±1.05	4.9±0.13	0.53±0.07
F4	111.09±0.70	3.9±1.09	4.5±0.10	0.36±0.05
F5	111.89±0.50	3.6±1.37	4.9±0.10	0.51±0.07
F6	110.34±0.20	3.8±1.11	4.7±0.10	0.47±0.09
F7	110.23±0.60	3.9±1.61	4.8±0.15	0.44±0.02
F8	109.12±0.50	3.7±0.3	4.7±0.15	0.57±0.02
F9	110.23±0.48	3.8±0.45	4.6±0.19	0.46±0.02
F10	110.24±0.20	3.6±0.25	4.5±0.21	0.57±0.07
F11	111.45±0.97	3.7±0.70	4.8±0.10	0.56±0.05
F12	112.03±0.54	3.9±0.25	4.9±0.15	0.53±0.08
F13	111.04±0.30	3.8±0.60	5.2±0.18	0.52±0.09
F14	108.23±0.35	3.7±0.56	4.9±0.10	0.42±0.02
F15	109.34±0.25	3.9±0.70	4.9±0.08	0.5 1±0.20
F16	111.12±0.55	3.8±0.40	4.8±0.21	0.58±0.9
F17	110.23±0.50	3.8±0.17	5.5±0.04	0.49±0.04
F18	111.67±0.30	3.8±0.40	4.8±0.14	0.52±0.03
F19	109.13±0.45	3.7±0.17	4.5±0.12	0.54±0.01
F20	109.45±0.55	3.9±0.96	4.9±0.10	0.63±0.03
F21	108.12±0.70	3.8±0.50	4.8±0.12	0.66±0.03
F22	111.45±0.80	3.7±0.63	4.5±0.10	0.52±0.015
F23	110.23±0.55	3.7±0.78	4.9±0.17	0.56±0.04
F24	110.12±0.60	3.8±0.86	4.9±0.14	0.53±0.06
F25	109.14±0.75	3.7±0.57	4.7±0.15	0.57±0.07
F26	110.18±0.15	3.9±0.63	4.9±0.18	0.52±0.03
F27	111.23±0.75	3.9±0.98	5.3±0.05	0.59±0.04

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

***In vitro* Dissolution Studies:**

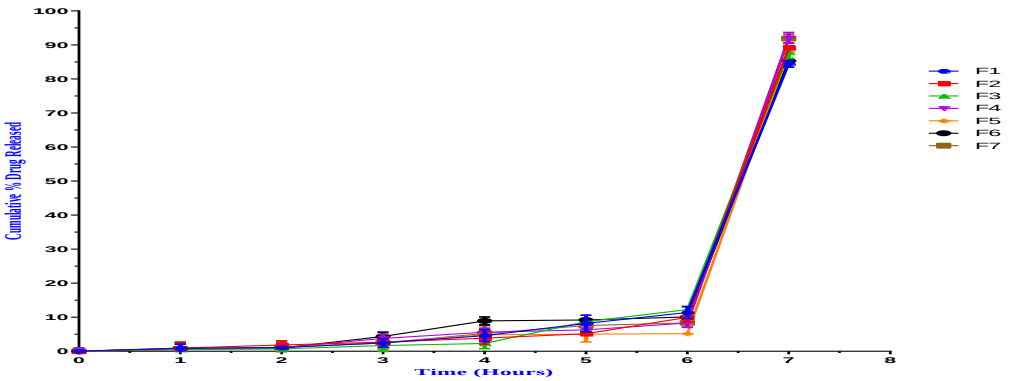

Figure 4: *In vitro* Drug Release Profile for colon ivermectin tablets F1-F7

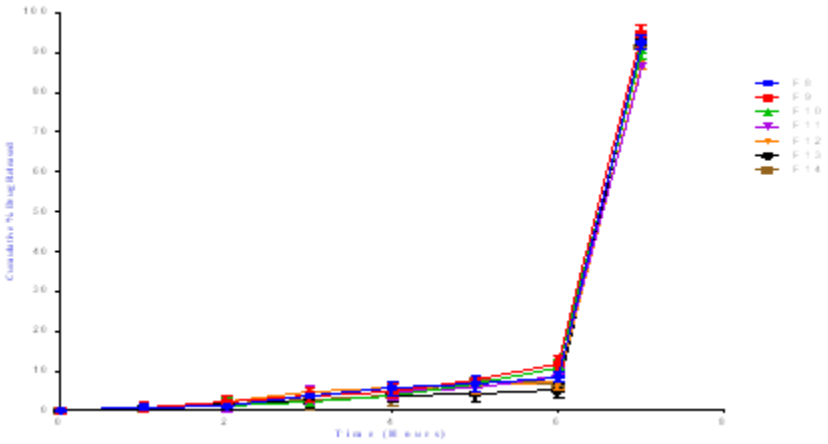

Figure 5: In vitro drug relase profile for colon ivermectin tablets f8-f14

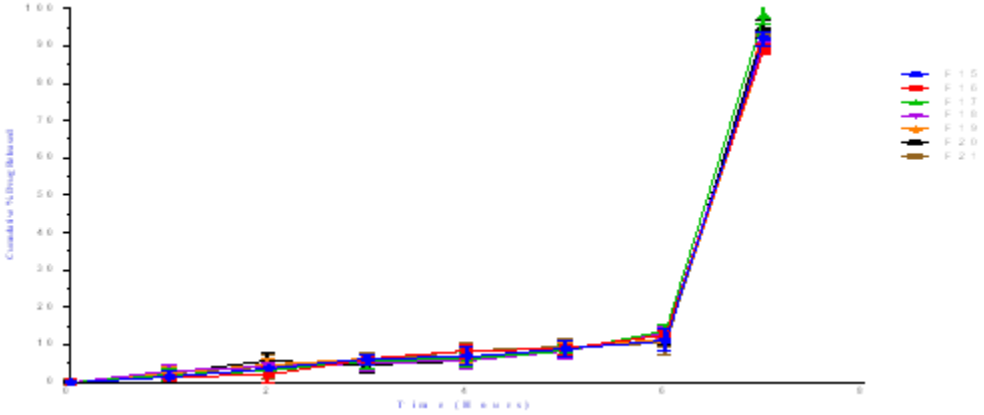

Figure 6: *In vitro* Drug Release Profile for colon ivermectin tablets F15-F21

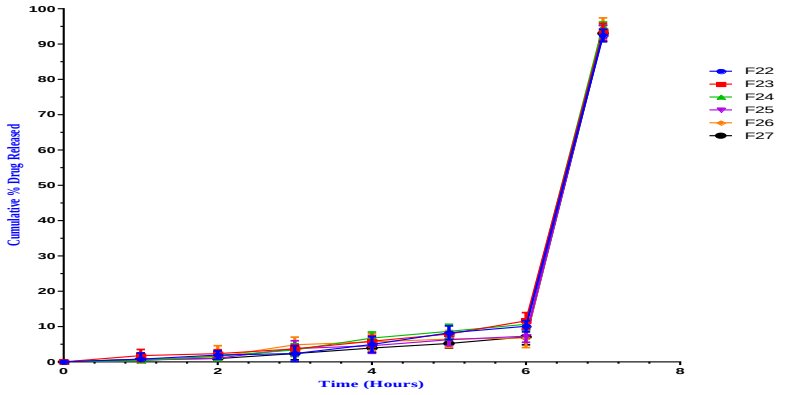

Figure 7: *In vitro* Drug Release Profile for colon ivermectin tablets F22-F27

In vitro drug release studies

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

The formulation with drug superdisintegrants ratio F17 was selected as optimized formulation

because it showed a maximize release in proximal colon.

Table: Comparison of marketed product with optimized formulation (F17)

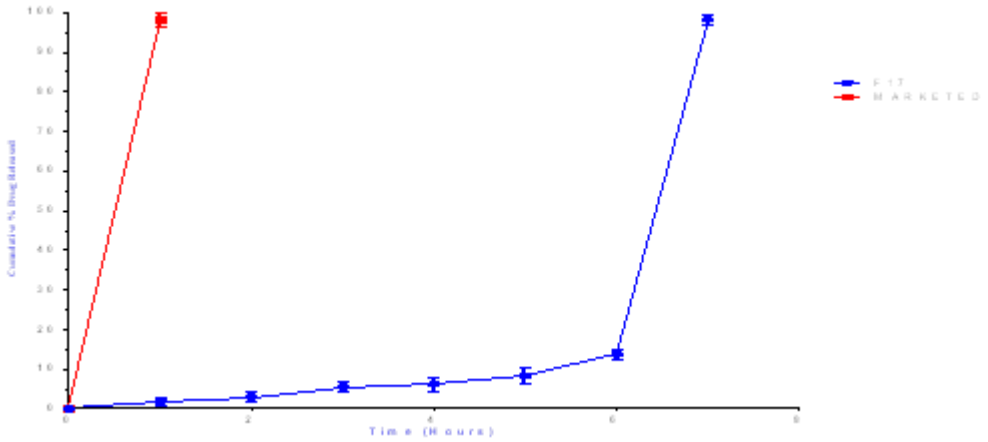

Figure 8: Comparative *In vitro* study plot of optimized formulation (F17) and conventional marketed tablet

Mathematical modeling of optimized formula of ivermectin 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 relese 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 relese kinetics of specific classes of controlled-relese 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 relese data to mathematical models.

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

In vitro drug release order kinetics for optimized (F17) Formulation

Table 9: Release kinetics of optimized formulation of ivermectin colon tablets

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer-Peppas	
	R^2	n	R^2	n	R^2	n	R^2	n
F17	0.994	8.02	0.842	0.119	0.946	29.41	0.988	0.817

From the above results it is apparent that the regression coefficient value closer to unity in case of zero order plot i.e.0.994 indicates that the drug release follows a zero order mechanism (Table 9).

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.

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 Korsmeyer-Peppas plots i.e. 0.817 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion.

In vitro drug release order kinetics for marketed product

Table 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	0.923	4.87	0.967	0.088	0.925	27.05	0.945	0.823

From the above results it is apparent that the regression coefficient value closer to unity in case of First order plot i.e.0.967 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.

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. 0.823 indicating non Fickian (anomalous) transport thus it projected that delivered its active ingredient by coupled diffusion and erosion.

Correlation Coefficient Values For Optimized

Table 11: Regression coefficient (R^2) & n values

S. No	Formulation	Zero order	First order	Higuchi model	Korsmeyer-Peppas model	n
1	**F17**	0.994	0.847	0.956	0.988	0.817
2	**Marketed**	0.923	0.967	0.925	0.945	0.823

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 11/ The optimized formulation was best fitted in Zero Order and Korsmeyer-Peppas. The optimized formulation n value was 0.817 indicating non Fickian (anomalous) transport thus it projected that 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.

Stability study

Table 12: Parameters after Accelerated Stability Study of Formulation F17

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 (%)	99.94±0.14	99.83±0.68	99.70±0.37	99.62±0.22
***In Vitro* Drug Release (%)**	98.21±1.15	98.17±1.53	98.15±1.42	98.11±1.35
Disintegration tests	37±0.64	37±0.56	36±0.67	36 ±0.23
Hardness	4.7±0.84	4.7±0.34	4.7±0.25	4.7±0.13

There were no physical changes in appearance and flexibility. After subjecting the optimized formulation (F17) to the Accelerated Stability Studies, the results were shown that there were no major changes in Drug Content, *In Vitro* Drug Release, Disintegration tests and Hardness. Hence the formulation was found to be stable.

SUMMARY AND CONCLUSION

In present work attempt was made to formulate and evaluate colon tablets of ivermectin. Attempts were made to achieve immediate drug release from the dosage form. Twenty seven formulations (F1-F27) were prepared by direct compression method using 3^3 Response surface method where 3^3 indicates 3 variables and 3 levels of natural superdisintegrants like Gellan Gum, Locust bean Gum and Fenugreek seed Gum (low, middle and high concentrations) by using Design of experiment software. In the Preformulation properties was 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 natural superdisintegrants by direct compression method and all formulations were coated by Eudragit RS 100 coating solution which is a pH sensitive polymer to prevent drug release in stomach and intestine. Entire drug will release in proximal part of colon. The formulation F17 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 F17 within 7 Hrs. Based on the physico-chemical properties and *in vitro* drug release, the formulation F17 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^{0}C) and humidity conditions (75 ± 5%RH) were seen. Hence the developed formulation was found to be stable even after subjecting to accelerated stability conditions. In the present work, it can be concluded that the colon Tablets of ivermectin formulations can be an innovative and promising approach for the delivery of ivermectin for the treatment of worm infections.

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