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Formulation and *In vitro* evaluation of colon targeted mesalazine tablet for the treatment of chronic pancreatitis

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A B S T R A C T

In the present research work sustained release matrix formulation of Mesalazine targeted to colon by using various polymers developed. To achieve pH-independent drug release of mesalazine, pH modifying agents were used. Colon targeted tablets were preparedin two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.

Keywords: Mesalazine, Colon targeted drug delivery system, Ethyl cellulose, Eudragit L100, Eudragit S 100

A R T I C L E I N F O

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1. Introduction

The Seriousness from constipation and diarrhea to the debilitating inflammatory bowel diseases (Ulcerative colitis and Crohn's disease) through to colon carcinoma which is two third cause of cancer in both man and women. Colon can be utilized as portal for the entry of drugs into the blood stream for the systemic therapy. Colon having the lower

level of luminal and mucosal digestive enzymes as compared with the small intestine reduces the chances of drug degradation. E.g.to facilitate absorption of acid and enzymatically labile materials especially proteins and peptides[1]. Colon delivery also a mean of achieving chronotherapy of disease that is sensitive to circadian rhythm such as asthma and arthritis Targeted delivery ensures the direct treatment at the disease site, lower dosing, and reduction in side effects. Colonic drug delivery is also found useful for improving systemic absorption of drugs like nitr-endipine (calcium channel blocker), metoprolol (anti-hypertensive), iso-sorbide mononitrate (anti-anginal). While in the colon, the low fluid environment and viscous nature of luminal contents may hinder the dissolution and release of the drug from the formulation. Moreover, the resident colonic microflora may impact on the stability of the released drug via metabolic degradation. In spite of these potential difficulties, a variety of approaches have been used and systems have been developed for the purpose of achieving colonic targeting. Targeted drug delivery is reliant on the identification and exploitation of a characteristic that is specific to the target organ. In the context of colonic targeting, the exploitable gastrointestinal features include pH, transit time, pressure, bacteria and prodrug approach [2].

Anatomy and Physiology of Colon:

The GIT is divided into stomach, small intestine and large intestine. The large intestine extending from the ileo-caecal junction to the anus is divided into three main parts. These are the colon, the rectum and the anal canal. The location of the parts of the colon is either in the abdominal cavity or behind it in the retro-peritoneum. The colon itself is made up of the caecum, the ascending colon, the hepatic flexure, the transverse colon, the splenic flexure, the descending colon and the sigmoid colon. It is about 1.5 m long, the transverse colon being the longest and most mobile part and has a average diameter of about 6.5 cm. The colon from the cecum to the splenic flexure (the junction between the transverse and descending colon) is also known as the right colon [3].

Available technologies based on the time controlled systems are:

1. **Codes system:** comprises a series of polymer s that are combined to protect the drug core until the formulation arrives in the colon [4].
2. **Colon-Targeted Delivery System -** uses lag time to achieve colon delivery. The system is comprised of three parts: an outer enteric coat, an inner semipermeable polymer membrane, and a central core comprising swelling excipients and an active component.
3. **Oros-CT:** is a technology developed by Alza Corporation and consists of an enteric coating, a semiper meable membrane, a layer to delay drug release, and a core consisting of two compartments.
4. **Time Clock - delivery device:** developed by Pozzi and colleagues is pulsed delivery system based on a coated solid dosage form.

Mesalazine is used in the treatment of anti-inflammatory agent, structurally related to the salicylates, which is active in inflammatory bowel disease. It is considered to be the active moiety of sulphasalazine. Although the mechanism of action of mesalazine is not fully understood, it appears to be topical rather than systemic [5]. Mucosal production of arachidonic acid metabolites, both through the cyclooxygenase pathways, i.e., prostanoids, and through the lipoxygenase pathways, i.e., leukotrienes and hydroxyl eicosatetraenoic acids, is increased in patients with chronic inflammatory bowel disease, and it is possible that mesalazine diminishes inflammation by blocking cyclooxygenase and inhibiting prostaglandin production in the colon.

2. Materials and Methods

Mesalazine (Natco Labs), Ethyl Cellulose (Signet Chemical Corporation, Mumbai, India.), Eudragit L-100, Eudragit S-100,Hydroxy Propyl Methyl Cellulose K100M, Magnesium stearate, Micro crystalline cellulose & Talc (Merck Specialities Pvt Ltd, Mumbai, India.), All other reagents used were of analytical grade.

Methodology

Drug - Excipient compatibility studies

Fourier Transform Infrared (FTIR) spectroscopy: The physical properties of the physical mixture were compared with those of plain drug. Samples was mixed thoroughly with 100mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12 psi for 3 minutes [6]. The resultant disc was mounted in a suitable holder in Perkin Elmer IR spectrophotometer and the IR spectrum was recorded from 3500 cm to 500 cm. The resultant spectrum was compared for any spectrum changes.

Preformulation parameters:

The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:

The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane [7]. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

$\tan \theta = h / r$ θ = Angle of repose

h = Height of the cone, r = Radius of the cone base

Bulk density: Density is defined as weight per unit volume. Bulk density, is defined as the mass of the powder divided by the bulk volume and is expressed as gm/cm^3. The bulk density of a powder primarily depends on particle size

distribution, particle shape and the tendency of particles to adhere together [7]. Bulk density is very important in the size of containers needed for handling, shipping, and storage of raw material and blend. It is also important in size blending equipment. 10 gm powder blend was sieved and introduced into a dry 20 ml cylinder, without compacting. The powder was carefully leveled without compacting and the unsettled apparent volume, Vo, was read.

The bulk density was calculated using the formula:

$$\text{Bulk Density} = M / V_o$$

Where, M = weight of sample

V_o = apparent volume of powder

Tapped density:

After carrying out the procedure as given in the measurement of bulk density the cylinder containing the sample was tapped using a suitable mechanical tapped density tester that provides 100 drops per minute and this was repeated until difference between succeeding measurement is less than 2 % and then tapped volume, V measured, to the nearest graduated unit [7]. The tapped density was calculated, in gm per L, using the formula:

$$Tap = M / V$$

Where, Tap= Tapped Density

M = Weight of sample

V= Tapped volume of powder

Measures of powder compressibility:

The Compressibility Index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities [7]. In theory, the less compressible a material the more flowable it is. As such, it is measures of the relative importance of interparticulate interactions. In a free- flowing powder, such interactions are generally less significant, and the bulk and tapped densities will be closer in value. For poorer flowing materials, there are frequently greater interparticle interactions, and a greater difference between the bulk and tapped densities will be observed. These differences are reflected in the Compressibility Index which is calculated using the following formulas:

$$\text{Carr's Index} = [(tap - b) / tap] \times 100$$

Where, b = Bulk Density

Tap = Tapped Density

Formulation development of Tablets:

Mesalazine colon targeted tablets were prepared by using compression coating technology. Initially internal core tablet containing drug and super disintegrate was formulated [7]. For the prepared core tablet compression coating is done by using various compositions of polymers. Ethyl cellulose, Polymethacrylate polymers such as Eudragit L100 and Eudragit S100 are used as polymers for compression coating. Tablets are developed in two stages

1) Preparation of core tablet containing drug and super disintegrate.
2) Compression coating of prepared core tablets.

Formulation of core tablet:

The core tablets are formulated by using 250 mg of drug molecule, sodium starch glycollate as super disintegrate, Micro crystalline cellulose as diluent, talc and magnesium stearate as Glidant and Lubricant respectively [8]. The composition of core tablet was given in below table 1.

Table 1: Composition of core tablet

Ingredient Name	Quantity (mg)
Mesalazine	250
Sodium starch glycollate	31.25
Talc	5
Magnesium stearate	5
MCC pH102	108.75
Total weight	400

Total weight of core tablet was fixed as 400 mg. The tablets are prepared by using 9mm flat punch. Then the prepared core tablets are subjected to compression coating by using various compositions of polymers.

Formulation of compression coated tablets:

The prepared core tablets were subjected to compression coating by using various compositions [10] of polymers such as Ethyl cellulose, Eudragit L 100 and Eudragit S 100 as coating materials. The composition of coating layer is given in below table.2. Compression coating layer was divided into two equal portions i.e., 50mg of each quantity. Half of the quantity of powder blend was placed in the die cavity, core tablet was placed exactly in the middle of die cavity and then remaining quantity of powder blend was placed over the core tablet so that the powder blend should cover all the sides and top side of core tablet uniformly [11]. Then the tablets are compressed by using 10mm flat surfaced punch using 8 station tablet punching machine with the hardness of 4 - 4.5 kg/cm^2.Then the prepared compression coted tablets are evaluated for various post compression parameters as per standard specifications.

Evaluation of post compression parameters for prepared Tablets: The designed formulation compression coated 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 weight variation test would be a satisfactory method of deter mining the drug content uniformity. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the following table and none deviate by more than twice the percentage [12]. The mean and deviation were determined. The percent deviation was calculated using the following formula.

$$\% \text{ Deviation} = (\text{Individual weight} - \text{Average weight} / \text{Average weight}) \times 100$$

Hardness:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation [13].

Thickness:

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

Friability:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Preweighed tablets were placed in the friabilator [13]. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as

$$\% \text{ Friability} = [(W1-W2) / W] \times 100$$

Where, W1 = Initial weight of three tablets

W2 = Weight of the three tablets after testing

Determination of drug content:

Both compression-coated tablets of were tested for their drug content. Ten tablets were finely powdered quantities of the powder equivalent to one tablet weight of Mesalazine were accurately weighed, transferred to a 100 ml volumetric flask containing 50 ml water and were allowed to stand to ensure complete solubility of the drug [14]. The mixture was made up to volume with water. The solution was suitably diluted and the absorption was determined by UV –Visible spectrophotometer. The drug concentration was calculated from the calibration curve.

***In vitro* drug release studies**

Drug release studies of Mesalazine core tablets:

The core tablets containing 15mg Mesalazine of were tested in (pH 6.8), for their dissolution rates [15]. Dissolution studies were performed using USP paddle type sample of 5 ml was withdrawn and replaced with equal volume of fresh medium. The samples were analyzed spectrophotometrically at respective 270 nm.

Drug release studies of Compression coated Mesalazine tablets: The release of Mesalazine 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 [16]. 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 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions. Drug release was measured from compression coated Mesalazine tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm and 270 nm respectively. All dissolution runs were performed for six batch. The results were given with deviation.

Application of Release Rate Kinetics To Dissolution Data: Various models were tested for explaining the kinetics of drug release [17]. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero order, first order, Higuchi, and Korsmeyer-Peppas release model.

Zero order release rate kinetics: To study the zero order release kinetics the release rate data ar e fitted to the following equation.

$$F = K_o t$$

Where, 'F' is the drug release at time't', and 'K_o' is the zero order release rate constant. The plot of % drug release versus time is linear.

First order release rate kinetics: The release rate data are fitted to the following equation

$$\text{Log } (100-F) = kt$$

A plot of log cumulative percent of drug remaining to be released vs. time is plotted then it gives first order release.

Higuchi release model: To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = k\ t1/2$$

Where, 'k' is the Higuchi constant.

In higuchi model, a plot of % drug release versus square root of time is linear.

Korsmeyer and Peppas release model:

The mechanism of drug release was evaluated by plotting the log percentage of drug released versus log time according to Korsmeyer- Peppas equation. The exponent 'n' indicates the mechanism of drug release calculated through the slope of the straight Line.

$$M_t / M_\infty = K\ t^n$$

Where,

M_t / M_∞ is fraction of drug released at time 't', k represents a constant, and 'n' is the diffusional exponent, which characterizes the type of release mechanism during the dissolution process. For non-Fickian release, the value of n falls between 0.5 and 1.0; while in case of Fickian diffusion, n = 0.5; for zero-order release (case I I transport), n=1; and for supercase II transport, n > 1. In this model, a plot of log (M_t / M_∞) versus log (time) is linear.

Hixson-Crowell release model:

$$(100-Qt)^{1/3} = 100^{1/3} - KHC.t$$

Where, k is the Hixson-Crowell rate constant.

Hixson-Crowell model describes the release of drugs from an insoluble matrix through mainly erosion. (Where there is a change in surface area and diameter of particles or tablets).

3 Results and discussion

The present study was aimed to developing compression coated Mesalazine formulations for colon targeting using ethyl cellulose and enteric coating polymers like Eudragit L100 and Eudragit S 100. All the formulations were evaluated for physicochemical properties and invitro drug release studies. Mesalazine 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 7.4, the results of angle of repose and compressibility index (%)

ranged from 32.74±0.12 to 37.08±0.96 and 13.37±0.38 to 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 powder mixture has good flow properties. The formulation blend was directly compressed to tablets and *in-vitro* drug release studies were performed.

Quality Control Parameters For compression coted tablets: Tablet quality control tests such as weight variation, hardness, and friability, thickness, and drug release studies in different media were performed on the compression coated tablet. Total weight of tablet including core is 300 mg.

***In-Vitro* Drug Release Studies:**

The compression coated tablets containing 250mg of Mesalazine were tested in 6.8 pH phosphate buffer solution for their dissolution rates. The release of Mesalazine from compression 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 3 hours, as the average small intestinal transit time is about 3 hours, and finally enzyme-free simulated intestinal fluid (SIF, pH 6.8) was used upto 12 hours to mimic colonic pH conditions.

Drug release was measured from compression coated Mesalazine tablets, added to 900 ml of dissolution medium. 5 ml of sample was withdrawn every time and replaced with fresh medium, samples withdrawn at various time intervals were analyzed spectrophotometrically at 275 nm ,319 and 320 nm respectively. All dissolution runs were performed for six batches.

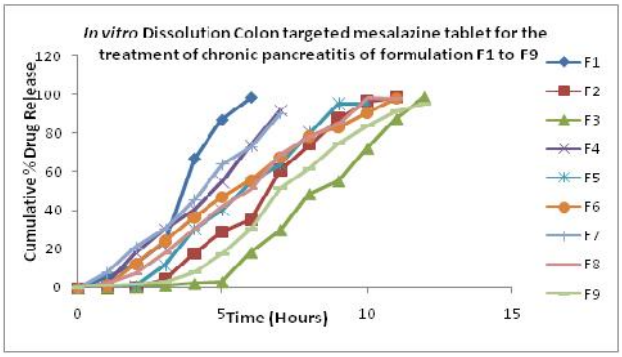

Figure 1: *In-Vitro* Dissolution Profile of Colon targeted mesalazine tablets of formulation F1 to F9.

From the dissolution values it was evident that the formulations F3 & F9 were retarded the drug release up to 12 hours, they shown drug release of 98.69 and 96.45 % respectively. Formulations F1 –F3 contains ethyl cellulose alone. As the concentration of ethyl cellulose increases retardation nature was increased.F3 formulation containing 150 mg of ethyl cellulose was show almost negligible amount of drug release in first 3 hours from the 5th hour onwards it shown drug release as the time proceeds slowly the polymer was undergone erosion and allowed the drug to come out from the dosage form. The formulation was retarded drug release up to 12 hours and it showed maximum drug release in 12 hours i,e., in colon region. Similarly the formulation F9 containing Eudragit L 100 in the concentration of 150 mg also showed similar drug release pattern.

Application of Release Rate Kinetics to Dissolution Data: Various models were tested for explaining the kinetics of drug release. To analyze the mechanism of the drug release rate kinetics of the dosage form, the obtained data were fitted into zero-order, first order, Higuchi, and Korsmeyer-Peppas release model.

4. Conclusion

In the present research work sustained release matrix formulation of Mesalazine targeted to colon by using various polymers developed. To achieve pH-independent drug release of Mesalazine, pH modifying agents (buffering agents) were used. Colon targeted tablets were prepared in two steps. Initially core tablets were prepared and then the tablets were coated by using different pH dependent polymers. Ethyl cellulose, Eudragit L100 and S100 were used as enteric coating polymers. The precompression blend of all formulations was subjected to various flow property tests and all the formulations were passed the tests. The tablets were coated by using polymers and the coated tablets were subjected to various evaluation techniques. The tablets were passed all the tests. Among all the formulations F3 formulation was found to be optimized as it was retarded the drug release up to 12 hours and showed maximum of 98.69% drug release. It followed zero order kinetics mechanism.

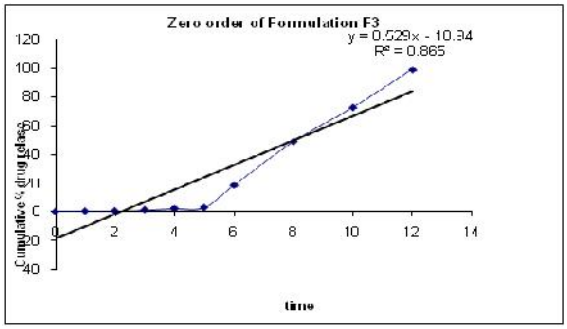

Figure 7 Zero order release kinetics graph

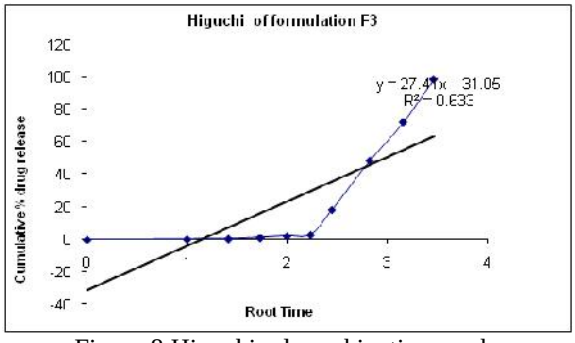

Figure 8 Higuchi release kinetics graph

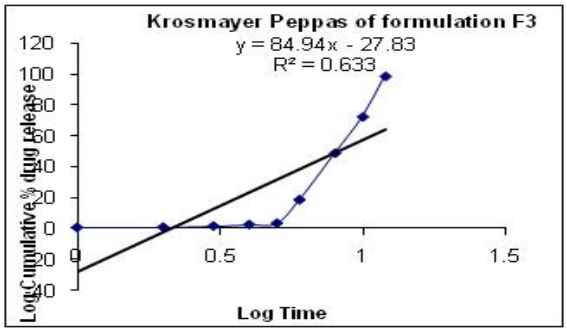

Figure No: 9 Kars mayer peppas graph

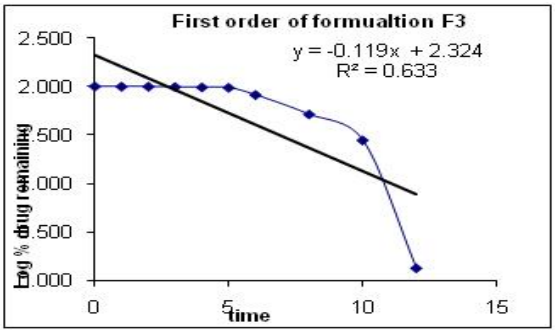

Figure: 10 First order release kinetics graph

Table 2: Composition of coating layer

Ingredient name	F1	F2	F3	F4	F5	F6	F7	F8	F9
Ethyl cellulose (mg)	25	50					25		25
Eudragit S100 (mg)			25	50			25	25	
Eudragit L100 (mg)					25	50		25	25
Magnesium stearate (mg)	3	3	3	3	3	3	3	3	3
Talc (mg)	3	3	3	3	3	3	3	3	3
MCC pH 102 (mg)	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Total weight	100	100	100	100	100	100	100	100	100

Table 3: Preformulation parameters of core material

Formulation Code	Angle of Repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's Ratio
F1	36.01	0.55	0.645	14.72	0.85
F2	34.8	0.57	0.66	13.63	0.86
F3	32.74	0.53	0.606	14.19	0.858
F4	35.33	0.531	0.613	13.37	0.866
F5	36.24	0.549	0.641	14.35	0.856
F6	36.12	0.564	0.666	15.31	0.846
F7	37.08	0.581	0.671	13.41	0.865
F8	35.12	0.567	0.654	13.12	0.845
F9	35.45	0.571	0.689	13.28	0.855

Table 4: Quality control parameters for compression coated tablets

Formulation codes	Weight variation (mg)	Hardness(kg/cm2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	512.5	4.5	0.52	4.8	99.76
F2	505.4	4.2	0.54	4.9	99.45
F3	498.6	4.4	0.51	4.9	99.34
F4	510.6	4.5	0.55	4.9	99.87
F5	309.4	4.4	0.56	4.7	99.14
F6	510.7	4.2	0.45	4.5	98.56
F7	502.3	4.1	0.51	4.4	98.42
F8	501.2	4.3	0.49	4.7	99.65
F9	598.3	4.5	0.55	4.6	99.12

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

Table 5: *In-vitro* Drug Release profile for coated formulations F1-F9

Time (hrs)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	5.42	0.26	0.34	2.39	1.11	1.44	8.06	2.65	1.32
2	12.65	0.44	0.54	17.88	1.29	12.30	20.94	7.23	2.14
3	23.56	4.65	1.26	30.45	11.71	24.44	30.26	18.19	2.90
4	66.8	17.87	2.22	40.59	30.22	36.61	45.44	30.27	8.11
5	86.9	29.18	3.05	55.01	40.18	47.30	63.86	42.06	17.72
6	98.35	35.45	18.41	73.85	54.53	55.68	72.93	51.40	30.40

7	--	61.04	30.05	91.92	63.88	67.53	90.23	69.13	51.64
8	--	74.24	48.69	--	80.53	78.72	--	78.45	61.59
9	--	88.13	55.38	--	95.06	83.34	--	85.67	74.97
10	--	96.39	72.34	--	95.18	90.67	--	98.45	84.18
11	--	98.45	87.56	--	--	98.12	--	98.12	91.87
12	--	--	98.69	--	--	--	--	--	95.45

Table 6A: Release kinetics data for optimised formulation

Cumulative (%) release q	Time (t)	root (t)	Log (%)release	log (t)	log (%) remain	Release rate (% release / t)
0	0	0	0		2.000	0
0.34	1	1.000	0.469	0.000	1.999	0.340
0.54	2	1.414	0.268	0.301	1.998	0.270
1.26	3	1.732	0.100	0.477	1.994	0.420
2.22	4	2.000	0.346	0.602	1.990	0.555
3.05	5	2.236	0.484	0.699	1.987	0.610
18.41	6	2.449	1.265	0.778	1.912	3.068
48.69	8	2.828	1.687	0.903	1.710	6.086
72.34	10	3.162	1.859	1.000	1.442	7.234
98.69	12	3.464	1.994	1.079	0.117	8.224

Table 6B: Release kinetics data for optimised formulation

1/cum% release	Peppas log q/100	% drug remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	100	4.642	4.642	0.000
2.9412	-2.469	99.66	4.642	4.636	0.005
1.8519	-2.268	99.46	4.642	4.633	0.008
0.7937	-1.900	98.74	4.642	4.622	0.020
0.4505	-1.654	97.78	4.642	4.607	0.035
0.3279	-1.516	96.95	4.642	4.594	0.048
0.0543	-0.735	81.59	4.642	4.337	0.304
0.0205	-0.313	51.31	4.642	3.716	0.926
0.0138	-0.141	27.66	4.642	3.024	1.617
0.0101	-0.006	1.31	4.642	1.094	3.547

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