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Fabrication of Layered Tablet of Curcumin With Natural Excipients For Colon Targeting

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ABSTRACT

The prominence of side effects or adverse reactions due to the existing drugs and polymers paved a need for the researchers to explore and investigate dietary substances and natural raw materials for therapeutic benefits. The current research was focused to fabricate and optimize layered colon targeted tablet of curcumin using natural excipients. Layered tablet was formulated using mucoadhesive polymers and enteric coating polymers. Compression coating technique was used to incorporate mucoadhesive polymers and dip coating technique was used for incorporating enteric polymers on curcumin loaded core tablets. Natural sources like Abelmoscus esculentus fruits, Hibiscus rosa-sinensis leaves, Artocarpus heterophyllus fruit, Linum usitatissimum seeds and Colocasia esculenta corms were used for extraction of mucoadhesive polymers. Natural ingredients like Starch, Pectin, Inulin and shellac were used as enteric coating polymers. In vitro dissolution studies for the optimized formulation was conducted using simulated dissolution media of pH 1.2 for first 2 h, pH 4.5 for further 2 h, pH 7.4 for another 2 h. The formulation containing 30% pectin, 10% shellac and 20% linum seed gum was found to reach the colorectal region with expected drug release. Thus, it's concluded that the optimized formulation makes a potential biodegradable colon targeted formulation for treating colorectal cancer, ulcerative colitis etc.

Keywords: Colon targeting, Natural excipients, Biodegradable, Mucoadhesive, Enteric polymers, Curcumin.

INTRODUCTION

Targeted drug delivery aids to deliver drug at the target site such that the effected tissue or region gets pinpoint treatment with minimal dose and extended time intervals. Drug targeting specifically to colon region is known as colon targeting [1]. Colon targeting can be achieved by two means i.e., through oral or through rectal route [2,3]. Oral route has better patient compliance, reduced side effects, flexibility in designing, lower dose compared to the rectal route. Among various approaches available for colon targeting pH sensitive polymer coated drug delivery with delayed release approach was selected for execution of the current work.

Polymers play a pivotal role in the design of a dosage form. A stable, non-toxic, economical and compatible dosage form can be achieved with the right choice of the excipients. Natural biodegradable polymers which are basically polysaccharides have gained much attention in view of their potential applications in various fields. Use of natural polymers instead of synthetic polymers aids in the development of a dosage form that is safer with minimal side effects specially in case of cancer [4,5].

Literature reveals many colon targeted drug delivery formulations of which are mostly formulated with synthetic excipients [6-11]. A few attempts were made by using natural excipients as part of the formulation [12-17]. In the present study an attempt was made to formulate a colon targeted dosage form with a natural origin drug/ active ingredient along with natural excipients i.e., colon targeted drug delivery system of Curcumin using natural polymers. Layered novel drug delivery system is implied for achieving colon targeting.

MATERIALS AND METHODS

Materials

Curcumin was obtained as a gift sample from Laila Neutraceuticals, Vijayawada, India. All the natural raw materials used for extraction of mucoadhesive polymers were obtained from local market. All other synthetic chemicals used in formulation were obtained from Merk, Mumbai.

Processing and characterization of mucoadhesive polymers

Abelmoscus esculentus fruits [18] (M1), Hibiscus rosa-sinensis leaves [19] (M2), *Artocarpus heterophyllus* fruit [20] (M3), Linum usitatissimum seeds [21] (M4) and *Colocasia esculenta* corms [22] (M5) were used as raw materials. All the raw materials collected were processed to remove superficial impurities. The selected plant part was processed individually for extraction of mucoadhesive portion using the following procedure [23].

- Selection of plant part having mucoadhesive portion.

- Cleaning, drying, grinding and sieving the selected plant part.
- Stirring and soaking the powdered portion in distilled water.
- Heating the supernatant solution and addition of 3 times the volume acetone.
- Washing the precipitated material with distilled water and drying at 40-50°C under vaccum.

All the extracted mucoadhesive portions were subjected to preliminary evaluation tests like Molisch's test, Iodine test, Enzyme test and Ruthenium test. Further evaluation of the extracted polymers were performed using swelling studies, Mucoadhesive bond strength and wash off test.

Swelling index

Swelling studies were performed to estimate molecular parameters of the swellable polymers such as using USP type I dissolution apparatus (DS 8000). Mucoadhesive tablets were prepared using 300 mg of extracted mucoadhesive portions (M1 – M5). The tablets were initially weighed using an Essae electronic balance having sensitivity 1 mg. The tablets were added to dissolution basket. After predetermined time, the tablets were removed and placed on a butter paper to blot dry and the tablets were re-weighed [24]. The swelling index was calculated from the following formula. Table 1 gives the following results.

$$\text{Swelling Ratio} = \frac{\text{wt of table after swelling} - \text{wt of table before swelling)}}{\text{wt of table before swelling}}$$

Mucoadhesive bond strength

Mucoadhesive tablets prepared using 300 mg of extracted mucoadhesive portion were subjected to mucoadhesive bond strength test. The test was performed using modified digital balance apparatus [25] as shown in Figure 1.

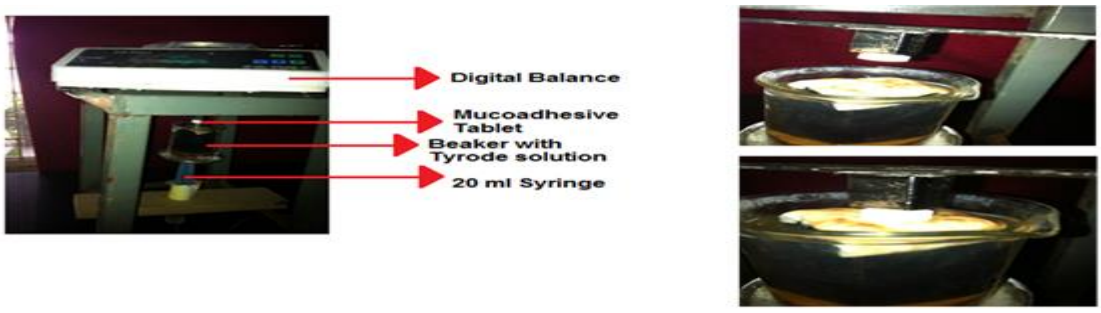


Figure 1: a) Modified electronic balance with hydraulic syringe system for measuring mucoadhesive strength of tablets (b) Mucoadhesive bond strength testing of formulations.

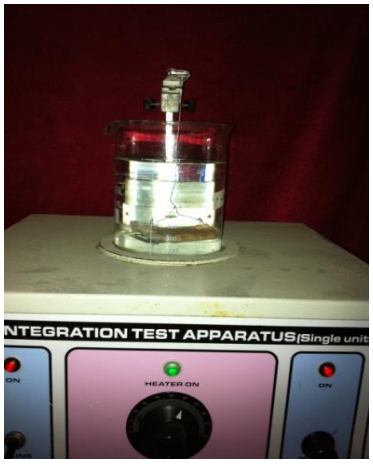
The apparatus works with hydraulic piston system. Pork stomach mucosa was used as model tissue. The tissue is immersed in Tyrodes solution maintained at 37 ± 0.5°C. The tablet attached to the iron strip by means of cynoacrylate gum was made to contact the mucosal layer by means of hydraulic syringe system. A pre-load of 20 mg was added for 5 min before the test. After removal of preload a negative force was applied which cause detachment of the tablet from the tissue? The force required to detach the tablet from the mucosal surface is noted down as weight (g) from the digital balance. From the weight obtained mucoadhesive strength and force of adhesion were calculated using the following equations and the results were tabulated in Table 2.

$$\text{Force of Adhesion(N)} = \frac{\text{Mucoadhesive strength(gm)X9.81}}{1000}$$

$$\text{Bond strength}\left(\text{N}/\text{M}^2\right) = \frac{\text{N}}{\text{Surface area of table}(\text{m}^2)}$$

Wash off test

This test was performed using modified USP Disintegration apparatus [25] shown in Figure 2. Live pork stomach mucosa was used as model tissue. Mucosal layer was mounted on the slides which were fixed to the arm of disintegration apparatus. Dissolution medium maintained at 37 ± 0.5°C was used for the entire study. The mucoadhesive tablets were placed on the mucosal tissue and the apparatus was allowed to make up and down strokes continuously. The time taken for the detachment of the tablet was noted down as wash-off period for the mucoadhesive formulations. The best mucoadhesive material was selected for compression coating on core tablet.

(a) 

(b) 

Figure 2: (a) and (b) Modified disintegration apparatus for wash off test.

Processing and characterization of enteric coating polymer

Enteric coating formulations were mixed homogenously as per the formula shown in Table 3 the prepared dispersions were laid on a glass slab as shown in Figure 3. The formed films as shown in figure were evaluated for tensile strength, folding endurance and water vapor permeation ratio.

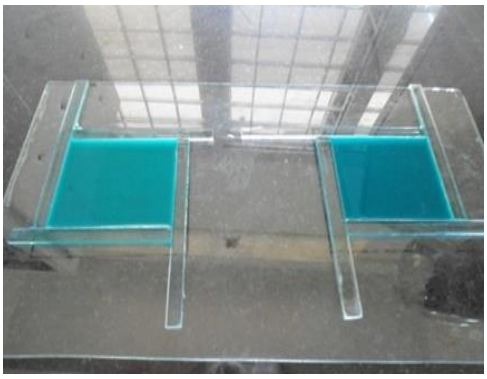
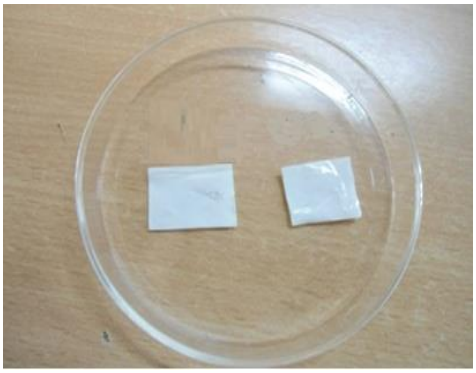
(a)  (b) 

Figure 3: (a) 7 × 7 cm films of enteric coating formulations poured on glass slab (b) Films formed using enteric coating formulations

Tensile strength

Tensile strength of the prepared enteric films was evaluated using tensiometer (Tensitron inc.). The film strips of dimension 5 × 5 were placed between the plungers and the force required to break the film was noted from the dial reading.

Folding endurance

A 5 × 5 dimension strip of the formed enteric film was folded repeatedly at the same place till it broke. The number of folding required to break the film was noted as folding endurance value.

Water vapor permeation test

Pre weighed enteric films were placed in the desiccators containing saturated solution of potassium chloride at room temperature [26]. Films were re-weighed after 24 hrs and the percentage water permeation was calculated using the formula mentioned below

$$\text{Percentage water vapour uptake} = \frac{\text{Final film weight - Initial film weight}}{\text{Initial film weight}} X100$$

The best enteric coating formulation was selected for coating on optimized mucoadhesive tablet.

Fabrication of layered tablet

Fabrication of layered tablets was done schematically as shown in Figure 4.

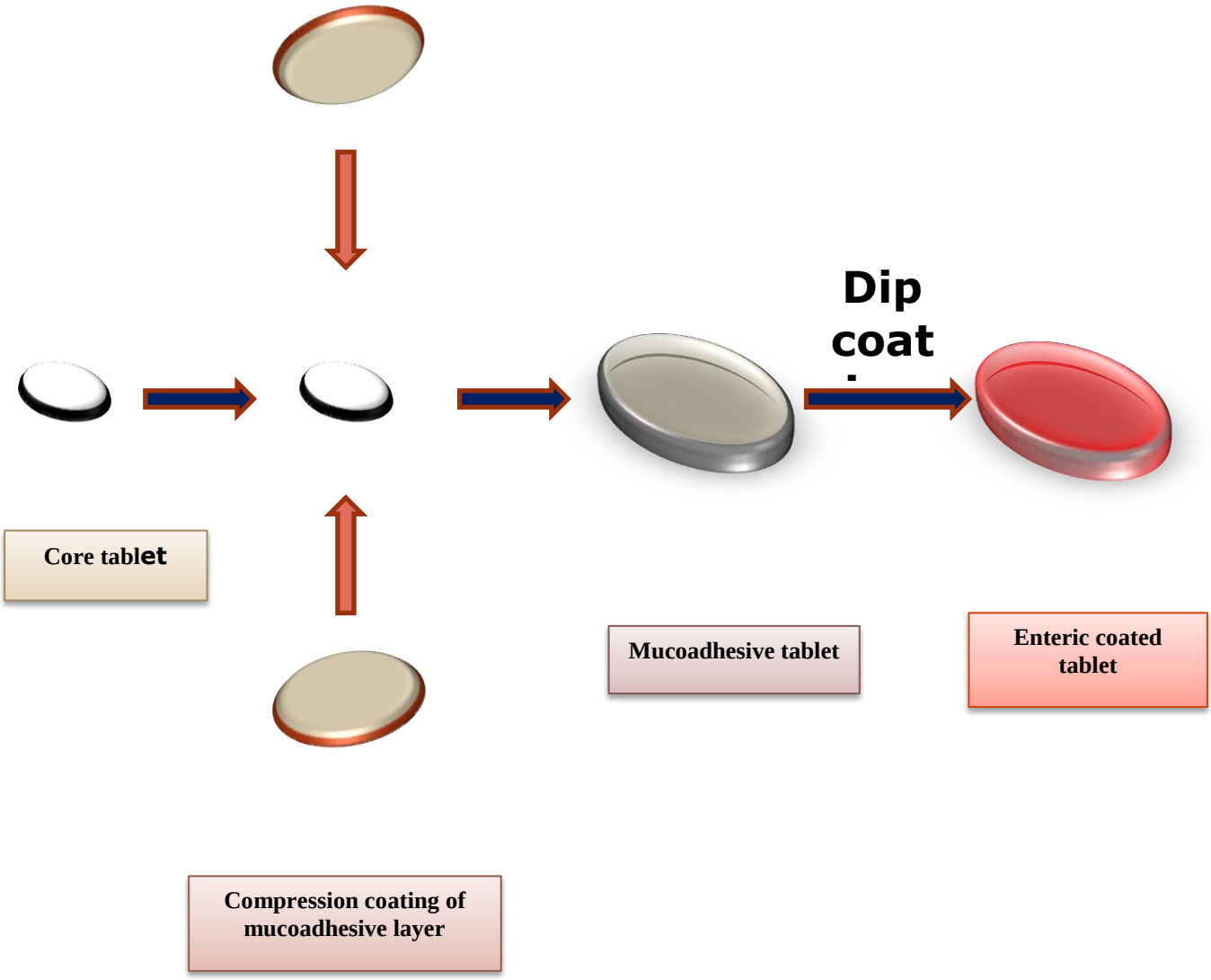


Figure 4: Schematic representation of fabrication of layered tablet

Core tablets were developed by direct compression method. All the ingredients as shown in Tables 4 and 5 were weighed separately and accurately. All the weighed ingredients were milled and passed through sieve no. 60. The sieved ingredients were blended to obtain a homogenous tablet blend. The prepared blend was compressed using 10 station rotary tablet press containing 9 mm round flat punches.

The optimized mucoadhesive portions of weight 300 mg were weighed accurately sieved and separated into 2 equal portions. First half portion is placed into the die cavity of 13 mm punch. The prepared core tablet is carefully placed manually at the centre in the die cavity. The other portion of the mucoadhesive material is placed carefully on the top of the core tablet into the die cavity and compressed to obtain mucoadhesive tablet containing core tablet.

The obtained mucoadhesive tablets were subjected to enteric coating by dip coating technique. The enteric polymers were weighed or measured accurately, blended together to form a homogenous mixture. The prepared mucoadhesive tablets were dipped carefully into the enteric coating solution dried using hot air. The coating process is continued until a weight gain of 2.5% is obtained.

In vitro characterization of prepared enteric coated tablets

The prepared enteric coated tablets as shown in Figure 5 was subjected to various *in vitro* evaluation tests as mentioned below

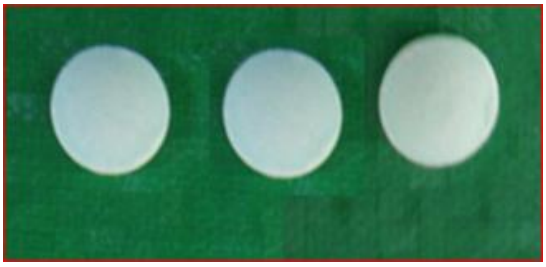


Figure 5: Enteric coated tablets.

Hardness

Hardness of the prepared tablets was measured using Monsanto hardness tester.

Friability

Friability of the prepared tablets was measured using Roche Friabilator

Disintegration

Disintegration time was performed using USP 6 basket digital disintegration apparatus.

Acid uptake test

Enteric coated tablets were evaluated for their ability to protect from gastric fluid by acid uptake test. The pre-weighed enteric coated tablets were placed in simulated gastric fluid of pH 1.2. After 4 hr the tablets were removed and observed for visual changes. The excess moisture was blotted using tissue paper and the tablets were re-weighed. The acid uptake% was calculated using the following equation.

$$\%\text{Acid uptake} = \frac{\text{Final table weight-Initial table weight}}{\text{Initial table weight}} X100$$

Stability

Stability of the optimized formulation was performed using varied conditions of humidity (45% RH, 60% RH, 75% RH) and temperature (2-8°C, 25-30°C, 45-50°C) were used as stress conditions. The test was conducted for duration of 3 months and periodic evaluation of drug content and physical parameters was performed.

In-vitro drug release studies

In-vitro drug release or Dissolution study was carried out using USP dissolution test apparatus (II i.e. paddle type. The stirring speed was maintained at 75 rpm. A bowl temperature of 37 ± 0.5°C and a bath temperature of 37.5 ± 0.5°C were maintained throughout the study. A dissolution fluid of 900 ml volume was considered. Dissolution study was performed at varied pH conditions like 1.2 pH (0.1 N HCl) for 2 h, pH 4.5 (Phosphate buffer) for further 2 h, pH 7.4 (Phosphate buffer) for subsequent hours. A 5 ml sample was withdrawn after each time interval and perfect sink conditions were maintained (Figure 6).

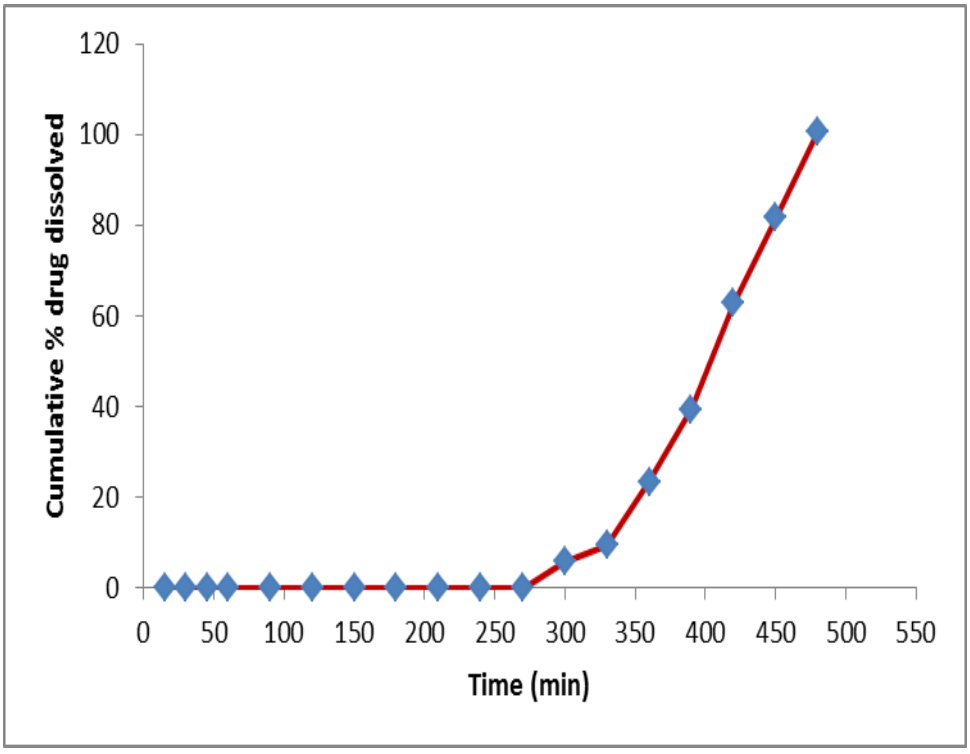


Figure 6: Dissolution profile

RESULTS AND DISCUSSION

Processing and characterization of mucoadhesive polymers

All the natural raw materials extracted were subjected to extraction to obtain dry mucoadhesive powders. The powders were evaluated preliminarily by Molisch's test, Iodine test, Enzyme test and Ruthenium test as per the procedure mentioned in Table 1. The results showed presence of carbohydrate, polysaccharide, mucilage and absence of enzymes. Thus it is concluded that the extracted material is pure mucilaginous substance. Further evaluation of the extracted mucoadhesive was performed using swelling index, mucoadhesive bond strength and wash off period tests.

Table 1: Preliminary evaluation of extracted mucoadhesive portions

S. No.	Name of the test	Result obtained	Inference
1	**Molisch's test**		
	100 mg dried mucilage + Molisch's reagent + conc. $H2SO4$ on sides of test tube	Violet green color obtained at the junction of 2 layers	Carbohydrates present
2	**Iodine test**		
	100 mg powder +1 ml 0.2 N $I2$ solution	No color observed in solution	Polysaccharide present (starch absent)
3	**Enzyme test**		
	100 mg dried powder + 20 ml distilled water + 0.5 ml Benzidine in alcohol	No blue color produced	Enzyme absent
4	**Ruthenium test**		
	100 mg dried mucilage powder + few drops ruthenium red solution; observe under microscope	Pink color produced	Mucilage present

Swelling index

Since all the extracted mucoadhesive have polysaccharide content, significant swelling was observed. As per the result mentioned in Table 2 swelling index value of all the mucoadhesive portions was found to be in the range of 14–52. Highest swelling index was observed for M4 mucoadhesive whereas least was observed for M5. Higher swelling index projects greater probability of adherence to the mucosal tissue [27].

Mucoadhesive bond strength

The mucoadhesive strength of all the tablets was found to be in the range of 18 – 39 g. Among all the mucoadhesive portions extracted M4 mucoadhesive was found to have maximum mucoadhesive strength of 38.5 g. Based on the mucoadhesive strength values, force of adhesion and bond strength values were calculated and were tabulated in Table 2.

Table 2: Mucoadhesive strength and wash off period values of various mucoadhesive portions

Mucoadhesive code	Swelling Index (%)	Mucoadhesive strength (g)	Force of adhesion (N)	Bond strength (N/m^2)	Wash off period
M1	28.17 ± 2.87	25 ± 1.2	0.245	542.58	1hr 12 min ± 9min
M2	39.44 ± 1.93	35 ± 0.82	0.343	759.62	2hr ± 7min
M3	43.64 ± 3.22	36 ± 0.18	0.353	781.32	2hr 15 min ± 5min
M4	52.22 ± 3.3	38.6 ± 0.75	0.378	837.75	2hr 50min ± 5min
M5	14.08 ± 2.41	18 ± 0.65	0.176	390.66	51 min ± 4min

Wash off test

The duration for which the tablet remained undetached from the pork mucosal tissue was noted down as wash off period and was given in Table 3. Among all the 5 mucoadhesive portions extracted M4 mucoadhesive has maximum duration of about 2hr 50 min whereas M5 has least duration of about 51 min.

Table 3: Various enteric coating formulations.

Ingredient name (%w/w)	EC 1	EC 2	EC 3	EC 4	EC 5	EC 6
Pectin			10	10	20	30
Shellac		10		10	10	10
Inulin	10					
Glycerol	3	3		q.s.	q.s.	q.s.
Ethanol		Up to 100				
Triethyl citrate			2.5	2.5	2.5	2.5
Talc			50			
Water	Upto 100			q.s	q.s.	q.s.

Processing and characterization of enteric coating polymer films

The enteric coating solution (EC1 – EC6) films formed using various concentrations of natural polymers like Pectin, Shellac, and Inulin were evaluated by means of various evaluation tests like tensile strength, folding endurance and water vapor permeation test. The results were shown in Table 4. The films formed using pectin, shellac and inulin alone were fragile and have very less tensile strength folding endurance and water permeation ratio. The reason might be lack of sufficient hydrophobicity and bonding forces between the polymer molecules. The films formed using combination of pectin and shellac showed good consistency, strength and stability compared to the films formed using the polymers alone. The reason might be the increase in cohesive bonding forces and balance between hydrophilicity and hydrophobicity of both the polymers. Enteric films formed with 30% pectin and 10% shellac was found to be the best in all evaluation parameters and was selected for coating on optimized mucoadhesive polymers.

Table 4: Evaluation of enteric coating films

Enteric formulation code	Tensile strength	Folding endurance	Water vapor permeation test
EC 1	0.91 ± 0.13	296 ± 32	1.974 ± 0.004
EC 2	0.54 ± 0.19	211 ± 28	2.143 ± 0.003
EC 3	0.65 ± 0.17	284 ± 30	2.748 ± 0.005
EC 4	1.39 ± 0.06	432 ± 21	1.863 ± 0.002
EC 5	1.65 ± 0.03	538 ± 25	1.437 ± 0.004
EC 6	2.14 ± 0.04	687 ± 21	1.324 ± 0.002

In-vitro characterization of prepared enteric coated tablets

Enteric coated tablets (F6) were obtained by compression coating of optimized mucoadhesive portion (M4 i.e., linum seed gum) on Curcumin loaded core tablet followed by dip coating with enteric polymer solution containing 30% pectin and 10% shellac. The obtained tablets were evaluated for various *in vitro* evaluation parameters and the results were shown in Table 5 and 6. The result of all the evaluation parameters like hardness (3-5 kg/m^2), friability (<1%), disintegration,% drug content (80 – 120%), acid uptake test were found to be within limit according to USP. Since the tablets were enteric coated no disintegration was observed in the gastric pH media.

Table 5: Composition of various ingredients used in core tablet.

Ingredient	C1	Purpose
Curcumin	20	API
Acacia	35	Binder
Lactose	35	Diluent
Talc	5	Glidant
Magnesium stearate	5	Lubricant
Total weight	100 mg	--

Stability studies

Stability studies were conducted using varied conditions of humidity (45% RH, 60% RH, 75% RH) and temperature (2-8°C, 25-30°C, 45-50°C) for a duration of 3 months. The films were periodically observed for change in drug content and other physical changes. The enteric coated tablets showed no significant variation in physical characteristics and drug content at lower and room temperature conditions. Whereas a minimal decrease in drug content which was within limits was observed at elevated temperature and humidity conditions.

Table 6: *In-vitro* evaluation parameters of prepared enteric coated tablets

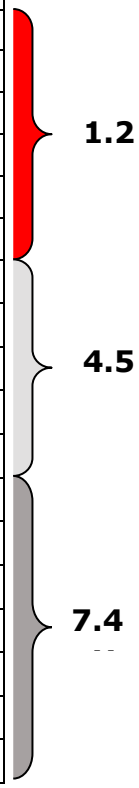
Parameters	F6
Hardness (kg/m^2)	4.2 ± 0.76
Friability (%)	0.006 ± 0.001
Disintegration	1.2 pH - Didn't disintegrate
	4.5 pH - > 2 hrs
	7.4 pH - < 60 min
% drug content	100.01 ± 1.05%
Acid uptake test	0.131 ± 0.004%
Stability (Assay after 3 months)	99.99 ± 1.13%

In-vitro drug release study/Dissolution study

From the intro drug release data shown in Table 7, it was found that the finalized enteric coated tablet showed no drug release in gastric pH (1.2 pH) and upper intestine pH (pH 4.5).

Table 7: Dissolution data in various pH media

S. No.	Time (min)	Cumulative% drug dissolved
1	15	0
2	30	0
3	45	0
4	60	0
5	90	0
6	120	0
7	150	0
8	180	0
9	210	0
10	240	0
11	270	0
12	300	5.75 ± 0.15
13	330	9.46 ± 0.17
14	360	23.35 ± 1.43
15	390	39.39 ± 1.69
16	420	62.73 ± 1.63
17	450	81.62 ± 1.21
18	480	100.7 ± 1.77



The dissolution study was continued for duration of 8 hours where drug release slowly started after replacing with large intestine pH simulated gastric fluid media. Maximum drug (Curcumin) release can be anticipated to occur at colorectal region. The enteric coating and the mucoadhesive portion aided in protecting the dosage form from releasing the drug Curcumin into the stomach and upper intestine region. Thus the objective of targeting dosage form to colon region was fulfilled. Kinetic treatment of dissolution data mentioned in Table 8 showed that the drug release followed first order kinetics and fits it Peppas model of drug release.

Table 8: Drug release kinetics of formulation

Formulation	Zero order equation		1 st order equation		Higuchi equation		Peppas equation	
	K	R^2	K	R^2	n	R^2	K	R^2
F6	0.217	0.854	0.0026	0.971	5.165	0.892	0.438	0.991

CONCLUSION

Based on the trending results obtained the layered tablet of Curcumin can be considered as a potential dosage for colon targeting of Curcumin. The natural ingredients used in the formulation offer great advantage over synthetic ingredients in terms of absence of daily intake limit, nullified side effects and adverse reactions. The current dosage form is suitable for treating moderate problems like ulcerative colitis and severe problems like colorectal cancer. Since targeting to the specific site was achieved minimal doses of active ingredient would suffice the need of treatment. The method of preparation is economical and can be suitable for industrial scale up. The layered portion can be suitable for incorporating any other drug entity meant for colon targeting.

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