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Formulation and evaluation of colon specific drug delivery system using *Boswellia serrata* gum

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Abstract

The present research investigation carried out was aimed to develop colon drug delivery system using Natural gum of *Boswellia serrata*. Physicochemical properties of gum were studied like micrometrics properties, pH and viscosity. The matrix tablets were prepared by direct compression technique using Diclofenac sodium as a model drug and various concentration of the drug and polymer was used to choose the suitable concentration of gum to be used with drug for the colonic drug delivery. The prepared tablets were evaluated for weight variation, hardness, thickness, friability, % drug content, disintegration time, *in vitro* drug release. % Drug release was found as F1- 97.56 ± 0.13 % in 22hrs, F2-95.21 ± 0.01% in 22hrs, F3-94.82 ± 0.01 % in 23 hrs, F4-92.36 ± 0.12 % in 24hrs, F5-90.22 ± 0.16 % in 24hrs, F4 showed good result overall as compared to others. Stability study was carried out for optimized batch (F4) By exposing it to temperature 40°C ± 0.21°C and 75% ± 0.16% RH for 60 days.

Keywords: colon specific, *Boswellia serrata*, diclofenac sodium, microbial triggered

Introduction

Colonic drug delivery can be achieved by oral or by rectal administration. Rectal delivery forms (Suppositories and enemas) are not always effective because a high variability is observed in the distribution of drugs administered by this route. Suppositories are effective in the rectum because of the confined spread and enema solutions can only be applied topically to great diseases of the sigmoid and the descending colon [1]. Rectal administration offers the shortest route to target drugs to the colon. However, reaching the proximal part of the colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and hence compliance may be less than optimal. Therefore, the oral route is preferred for the treatment of diseases associated with part of proximal colon. Absorption and degradation of the active ingredient in the upper part of gastrointestinal tract is the major obstacle with the delivery of drug by the oral route and must be overcome for successful colonic drug delivery [2]. Colon-specific systems could also be used in conditions in which a diurnal rhythm is evident, e.g. asthma, rheumatic diseases, ulcers and ischemic heart diseases. The incidences of asthmatic attacks are for example, greatest during the early hours of the morning. As dosage forms remain longer in the large intestine than in the small intestine, colon-specific formulations could be used to prolong drug delivery [3-4].

Natural polysaccharides are extensively used for the development of solid oral dosage forms for colonic delivery of drugs. Biodegradable polymers are generally hydrophilic in nature and have limited swelling characteristic in acidic pH. Various bacteria present in the colon secrete many enzymes which can cause hydrolytic cleavage of glycosidic bonds e.g. C-D-galactosidase, amylase, pectinase, C-D-glucosidase, dextranase, D-D-xylosidase. These polymers are inexpensive and are available in a variety of structures. Pectin, starch, guar gum, amylase and karaya gum are a few polysaccharides commonly used in dosage forms. Linear polysaccharides remain intact in stomach and small intestine but the bacteria of human colon degrades them and thus make them potentially useful in colon targeted drug delivery systems [5-7].

Materials & Methods

Materials

Diclofenac Sodium was obtained as gift sample from Cipla Ltd. Mumbai., *Boswellia serrata* gum was isolated in Lab., Lactose, and Magnesium Stearate was purchased from Rankem Laboratories., All other materials used of analytical/pharmaceutical grades.

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Methods

Isolation of *Boswellia serrate* gum

The coarsely powdered oleo-gum resin was purified with water to remove the impurities, then oleo-gum resin was extracted with alcohol. The precipitated gum was filtered through muslin cloth and gum was dried in oven at 45 Celsius till it completely dried. The gum powdered was passed through 80# sieve and calculated percentage yield ^[8].

Physicochemical evaluation of *Boswellia serrata* Roxb. ex Colbr gum

Micromeritic Properties of gum

Flow properties of granules were determined by measurement of angle of repose, bulk density, tapped density, compressibility index (CI) and Hausner's ratio.

Viscosity of gum:- The viscosity of gum was measured by using the 2 - 12% w/v solution of gum. The result was collected in measure of cP (Poise) ^[9].

pH of gum:- The pH of gum was measured by using the 1% w/v solution of gum and measured on pH metre.

Drug & Excipients compatibility study

DSC study

Assessment of possible incompatibilities between an active drug substance and different excipients forms an important part of the Preformulation stage during the development of solid dosage form. Differential Scanning Calorimeter (DSC PerkinElmer 4000) allows the fast evaluation of possible incompatibilities, because it shows changes in the appearance,

shift of melting endotherms and exotherms, and/or variations in the corresponding enthalpies of reaction. The DSC thermograms of pure drug, other excipients and optimized film were recorded. The thermal analysis was performed in a nitrogen atmosphere at a heating rate of 10°C/min over a temperature range of 30°C to 350°C. DSC study was performed for Diclofenac sodium and physical mixture of all ingredients of Tablet preparation ^[10-11].

FT-IR Study

The FTIR of pure drug and physical mixture of formulation ingredients of optimized batch was measured using Fourier transform infrared spectrophotometer (Model FTIR- Agilent carry 630, United States). The amount of each formulation ingredient in the physical mixture was same as that in the optimized batch. The pure drug and physical mixture were then separately mixed with IR grade KBr. This mixture was then scanned over a wave number range of 4000 to 400 cm⁻¹ ^[12-13].

Preparation of tablet dosage form by direct compression

The matrix tablets containing 50 mg Diclofenac sodium were formulated with different proportions of natural gum polymer. Diclofenac sodium and all other ingredients were passed through sieve no 60. separately and mixed homogeneously. The powder was lubricated with a mixture of talc and magnesium stearate. Finally the lubricated powders were compressed into tablets containing 50 mg Diclofenac sodium using 8 mm concave punch. Prepared tablets to be evaluated on all the parameters as necessary to compile with the standard values.

Table 1: Formulations of Colon Tablets of Diclofenac sodium.

Sr. No.	Ingredients	F1	F2	F3	F4	F5
1.	Diclofenac sodium.(mg)	50	50	50	50	50
2.	Boswellia Gum.(mg)	50	75	100	125	150
3.	Lactose.(mg)	150	125	100	75	50
4.	Magnesium Stearate.(mg)	5	5	5	5	5
5.	Talc.(mg)	2.5	2.5	2.5	2.5	2.5
6.	Total Weight (mg)	257.5	257.5	257.5	257.5	257.5

Evaluation of Tablets

Tablet Thickness

The crown thickness of individual tablets is measured with Vernier Caliper. The crown thickness of individual tablets is also determined for the purpose of determining the density of tablet compacts ^[14].

Hardness

Hardness of the tablet is determined using Monsanto hardness tester. The tablet to be tested is placed between the spindle and anvil and pressure is applied by turning the knurled knob just sufficiently to hold the tablet in position. The reading of pointer on scale is then adjusted to zero. The pressure is now increased as uniformly as possible until tablet breaks. The pointer now reads the pressure required to break the tablet ^[15].

Weight Variation Test

Twenty tablets were accurately weighted and an average weight was calculated. Not more than two individual weights deviate from the average weight by the percentage deviation.

Friability

Twenty tablets were accurately weighed and placed inside the

chamber of friabilator. The apparatus was rotated for 100 revolutions. After rotations, the tablets were weighed and the loss in weight was determined. The loss in weighed should not be more than 1%.

$$\% \text{ Friability} = \frac{\text{Initial wt.} - \text{Final wt}}{\text{Initial wt}} \times 100.$$

Determination of Drug Content

Drug content from the tablet was determined by taking tablets from each formulation. Twenty tablets from each formulation were accurately weighed and powdered. Powder equivalent to 50mg of the drug was weighed and transferred into a volumetric flask using 100ml of 0.1N HCL. A suitable volume of filtrate was diluted with a sufficient of 0.1N HCL to produce a solution containing 10mcg of Diclofenac sodium. The absorbance was measured at 279nm ^[16].

In vitro Drug Release

In vitro drug release studies of matrix formulation were carried out using USP – 23 Basket type dissolution apparatus. Phosphate buffer 6.8 (900 mL) was dissolution medium at 100 ± 1 rpm in medium at 37 ± 0.5 °C. Release studies were carried out in dissolution medium with rat caecal content (4% w/v). A matrix formulation was transferred to the 900 mL

phosphate buffer (6.8 buffer) as dissolution medium. At predetermined time intervals, the samples were withdrawn from the dissolution medium and after suitable dilution and assayed at 279 nm. For simulating conditions of the GIT, drug release studies were also performed with 0.1 N HCl buffer (pH 1.2) for first 2hrs, phosphate buffer saline 6.8 for further study with rat caecal content (4% w/v) [17-18].

Accelerated stability studies

From the prepared dosage form, batch would which showed appropriate balance between the physical parameters and the percentage release was selected for stability studies. The Diclofenac sodium tablets (B) were placed in borosilicate screw capped glass containers and stored at temperature (40°C ± 2°C) with relative humidity (75% ± 5% RH) For a period of 15 days. The samples were assayed for drug content

at regular intervals of 60 days [19].

Result and Discussion

Micromeritic Study

The evaluation of *Boswellia serrata roxb. Colbr* gum was carried out on various physicochemical parameters such as Micrometric properties, Angle of repose was found to be 24.47° ± 0.32°, Bulk density was found to be 0.61 ± 0.01, Tapped density was found to be 0.75 ± 0.02, Carr’s Index was found to be 18.66 ± 0.01 which signify the good flow property of gum, Hausner’s Ratio was found to be 1.22 ± 0.01 and Viscosity of gum was measured by using various gum concentration and was found to be 2% = 1.5 cP, 4% = 2.10 cP, 6% = 3.60 cP, 8% = 8.70 cP, 10% = 13.5 cP. The pH of gum was 6.5 ± 0.50.

Table 2: Micromeritic Characteristics of Gum.

Sr. No.	Parameter’s	Observations
1.	Angle of Repose	24.47° ± 0.32°
2.	Bulk Density	0.61 ± 0.01
3.	Tapped Density	0.75 ± 0.02
4.	Carr’s Index	18.66 ± 0.01
5.	Hausner’s Ratio	1.22 ± 0.01

Viscosity of Gum: Viscosity of gum was measured by using the Brookfield Viscometer and result was obtained in cP unit. For the various percentage of solution such as 2% to 12% w/v solution.

Table 3: Viscosity of various gum concentrations.

Serial Number.	Viscosity (w/v)	Observations.
1.	2%	1.5 cP
2.	4%	2.10 cP
3.	6%	3.60 cP
4.	8%	8.70 cP
5.	10%	13.5 cP

pH of Gum:- The pH of gum was measured by using electronic pH meter and it was found to be 6.5-7.0 ± 0.50

Drug – Polymer Compatibility Study

Differential scanning calorimetry analysis

The pre-formulation study were performed by Differential Scanning Calorimetry (DSC) and found that there was no any interaction between Diclofenac sodium and excipients. By the Differential Scanning Calorimetry conclude that DS gives peak at 156.60 °C which has its Melting point peak which is correlate with formulation Melting point peak. So, there were no interaction between Drug and Polymers.

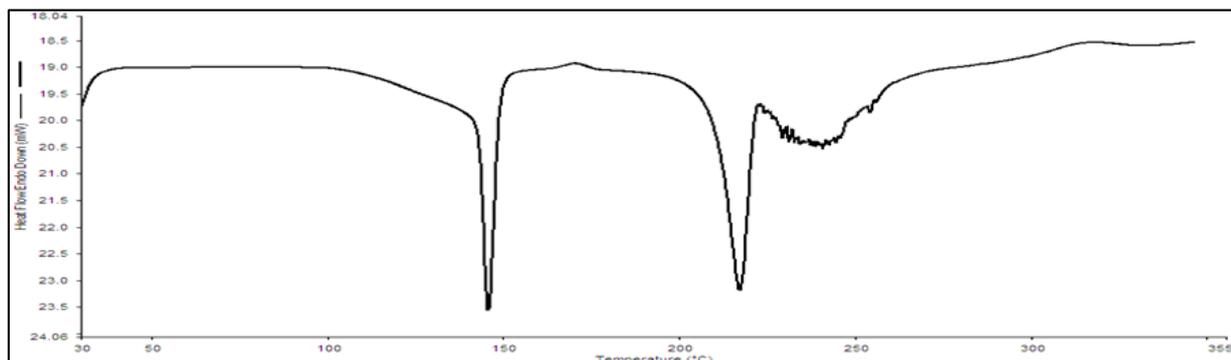


Fig 1: DSC of Diclofenac sodium.

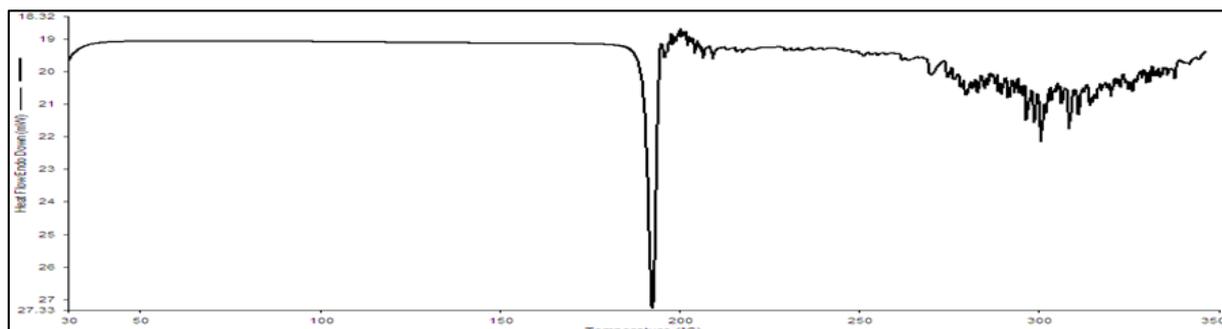


Fig 2: DSC of *Boswellia serrata Roxb. ex Colbr*.

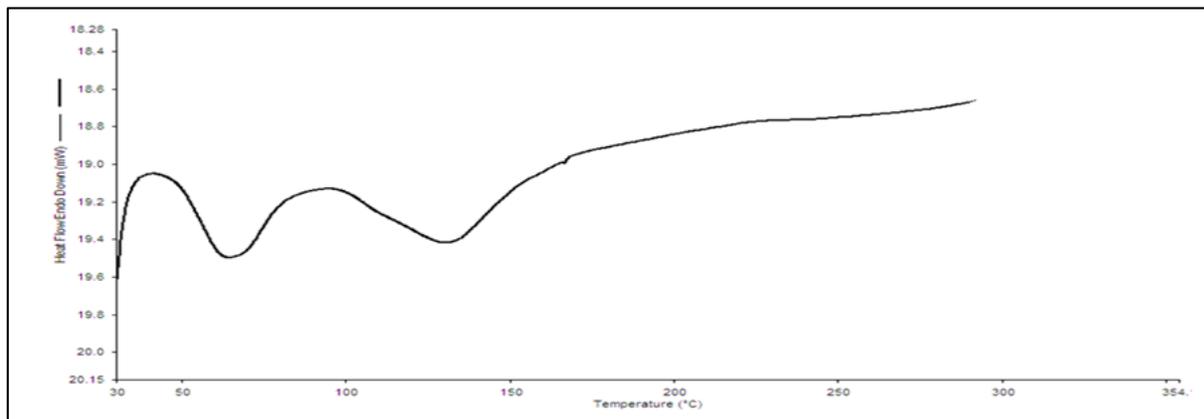


Fig 3: DSC of Physical mixture.

Infrared Spectroscopy Analysis

FT-IR spectrum was studied with drug and excipients all other as used in the formulation and there was no interaction

between the drug and polymers. It was found that the drug and polymers are compatible with each other.

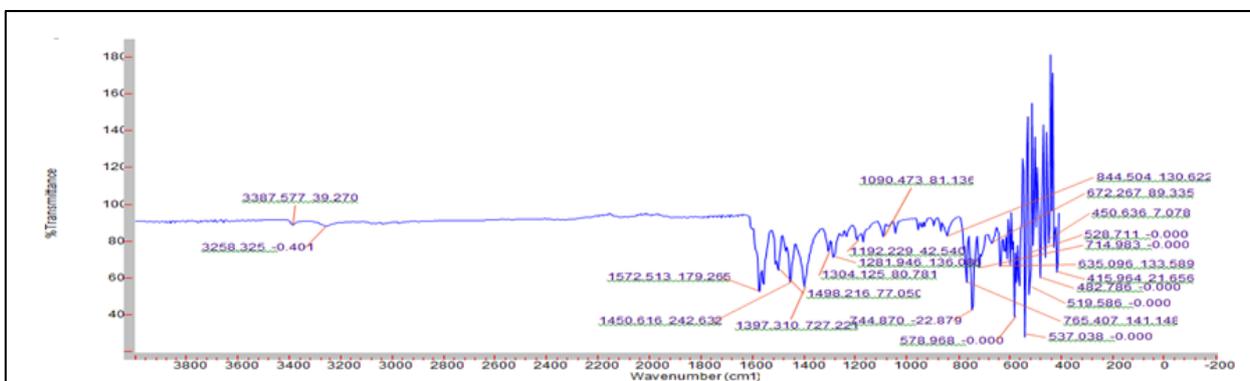


Fig 4: Diclofenac sodium IR Spectra.

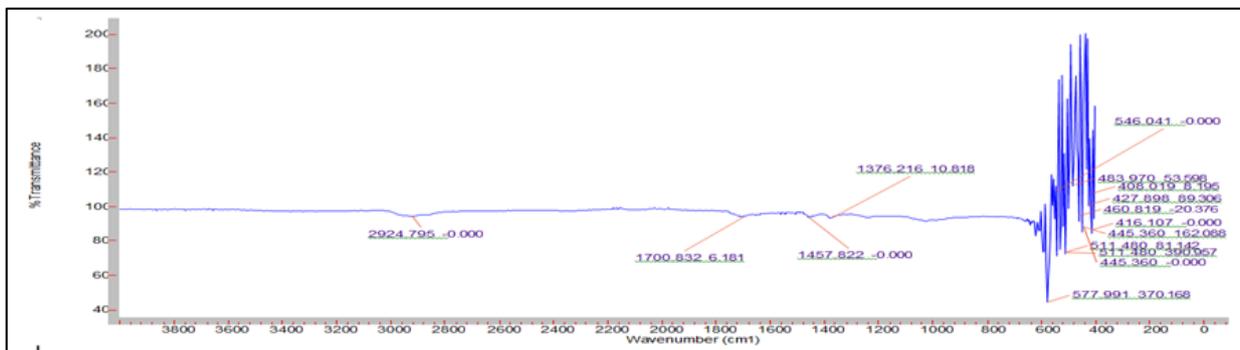


Fig 5: *Boswellia serrata* Roxb. ex Colbr Gum IR Spectra.



Fig 6: Drug + Gum Polymer.

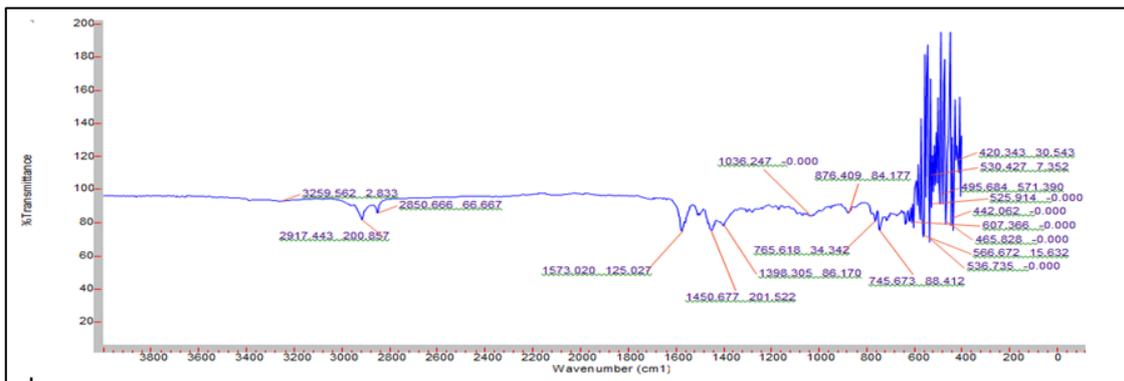


Fig 7: Physical Mixture.

Evaluation of diclofenac sodium colon – specific tablet. tablet thickness

The thickness of the tablets was found in the range $3.064 \pm 0.04 - 3.11 \pm 0.024$ mm. Uniform thicknesses was obtained due to uniform die fill. All values of all batches were in acceptable range.

Hardness

Hardness of the tablets was found in the range $5.21 \pm 0.27 - 5.69 \pm 0.33$ kg/ cm². Uniform hardness was obtained due to equal compression force.

Weight Variation

Tablets were prepared using Dry Granulation Method. Since the material was free flowing, tablets were obtained of

uniform weight due to uniform die fill. Tablets were obtained in the range with acceptable weight variation as pre pharmacopoeia specification, less than 5%.

Friability

Friability of tablets was observed in acceptable range $0.33 \pm 0.51 - 0.16 \pm 0.12$ (Less than 1%). These also support the Hardness was acceptable and within standard limits for prepared tablets.

Drug Content

The drug content of the tablets was found between $98.16 \pm 0.55 - 99.65 \pm 0.61\%$ of Diclofenac sodium tablet. The content uniformity test was performed to know the content of drug in each tablet of all formulation.

Table 4: Evaluation of various parameters.

Batch	Average Weight (mg) (\pm SD)	Thickness (\pm SD)	Friability (%) (\pm SD)	Hardness (\pm SD)	Drug Content (%) (\pm SD)
F1	257 ± 0.16	3.084 ± 0.04	0.33 ± 0.51	5.21 ± 0.27	96.00 ± 0.22
F2	259 ± 0.12	3.108 ± 0.02	0.46 ± 0.28	5.42 ± 0.20	98.16 ± 0.55
F3	258 ± 0.11	3.09 ± 0.021	0.20 ± 0.20	5.49 ± 0.22	98.42 ± 0.32
F4	257 ± 0.19	3.11 ± 0.024	0.13 ± 0.10	5.67 ± 0.15	99.32 ± 0.29
F5	255 ± 0.16	3.064 ± 0.04	0.16 ± 0.12	5.69 ± 0.33	99.65 ± 0.61

n=6

In vitro Drug Release

In Vitro Drug release studies was performed for all the formulations and release behavior was given in fig.no.- 8 dissolution study found that the F1 gives 97.56 ± 0.13 % in

22hrs, F2 gives 95.21 ± 0.01 % in 22hrs, F3 gives 94.82 ± 0.01 % in 23 hrs, F4 gives 92.36 ± 0.12 % in 24hrs, F5 gives 90.22 ± 0.16 % in 24hrs

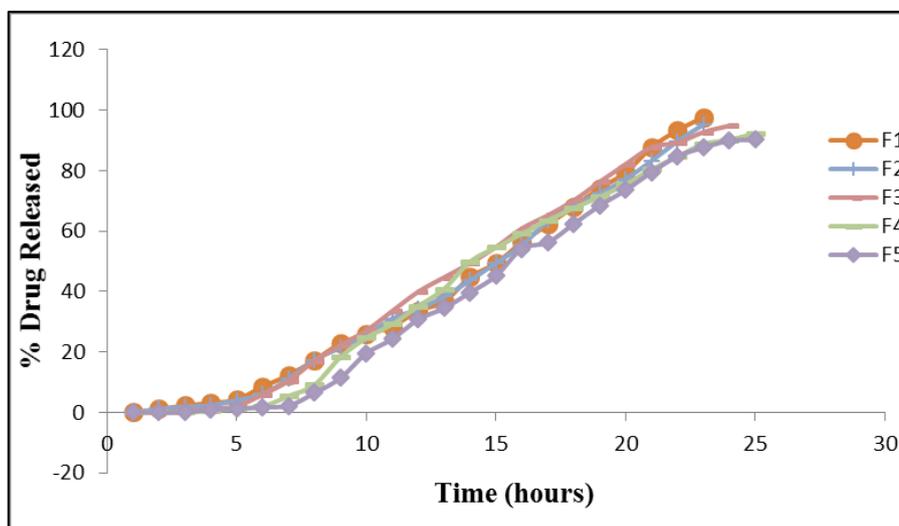


Fig 8: Graphical representation of %Drug released of tablet.

Accelerated Stability Study

Stability study was carried out for optimized batch (F4) By exposing it to temperature $40^{\circ}\text{C} \pm 0.21^{\circ}\text{C}$ and $75\% \pm 0.16\%$

RH for 60 days. The sample was analysed for drug content at the regular interval of 15 days. It was found that formulation F4 was stable for following temperature.

Table 5: Accelerated Stability Study

Parameters	0	15	30	45	60
Colour.	No Change.				
Hardness.	5.67 ± 0.15	5.67 ± 0.10	5.54 ± 0.09	5.12 ± 0.02	5.11 ± 0.07
Friability.	0.13 ± 0.10	0.13 ± 0.10	0.12 ± 0.12	0.12 ± 0.02	0.11 ± 0.06
Content uni.	99.32 ± 0.29	99.32 ± 0.06	98.89 ± 0.03	98.36 ± 0.03	98.02 ± 0.06
%Drug Rel.	92.36 ± 0.12	92.36 ± 0.12	92.32 ± 0.12	91.09 ± 0.05	91.01 ± 0.01

Stability was also confirmed by IR spectroscopic study of Formulation F4 after 60 days. The IR spectra was shown in

Fig. No. 26, it indicated that the formulation was stable for period of 60 days.

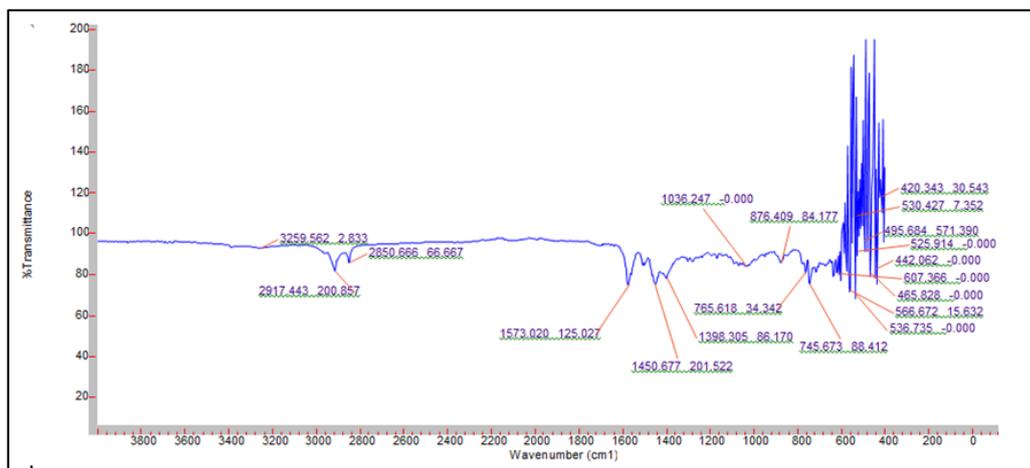


Fig 9: Optimized formulation IR spectra of F4.

Conclusion

It may be concluded from the present study that slow and controlled release of Diclofenac sodium over a period of 24 hours was obtained by using of Natural polymer *Boswellia serrata roxb. Colbr* was successful in the formulation of colon targeted tablet at the same time it is effective in retarding the drug release. Among all the formulations, F4 shows that overall good results.

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