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COLON DRUG DELIVERY OF BERBERIN HYDROCHLORIDE

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ABSTRACT

Many studies have been carried out on Berberin Hydrochloride (BBH) use for treatment of different diseases such as diabetes, GI infections, high cholesterol, high blood pressure, obesity and many more. This research gives the study colon targeting of BBH for treatment of Gut diseases. Inflammatory bowel disease treatment by use of colon targeting of BBH. Drug fabricated into retard dosage tested at different pH condition. Study confirms the use of natural gums in retardation of drug.

KEYWORDS: Berberin hydrochloride, Colon targeting, Treatment of bowel diseases.

INTRODUCTION

Colon Targeted Drug Delivery Systems (CTDDS)

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons;

(i) less diversity, and intensity of digestive enzymes,

(ii) Comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic

degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.

Ongoing research in the area of oral delivery of drugs, a discipline which has basked in the spotlight of pharmaceutical sciences for the past 70 years, has led to improved and profound insights into the physiology, biology and physical chemistry (pharmacokinetics, partitioning phenomenon) of organs, compartments, cells, membranes, cellular organelles and functional proteins (e.g. transporters) associated with absorption processes of drugs in the gastrointestinal tract (GIT). Majority of the research has focused on delivery of drug to the small intestine. The large intestine, however, because of its remoteness and relatively different physiology acquired the status of an outcast. From last two decades, interest in area development of oral colon targeted drug delivery systems (CTDDS) has increased, for treatment of local colonic disorders. 1 Colonic delivery offers several potential therapeutic advantages as a site for drug delivery,

(a) The colon is rich in lymphoid tissue, uptake of antigens into the mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.
(b) The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability.
(c) The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
(d) Reduced proteolytic activity in the colon may be helpful in achieving reasonable absorption of certain drugs that are enzymatically labile in small intestine.
(e) Reduced fluid motility and motility in the colon when compared with small intestine is advantageous formulation consists of multiple components such as permeation enhancers that must reach epithelial layer to achieve close spatial proximity with each other.
(f) The colonic region has somewhat less hostile environment with less diversity and less intensity of activity as compared to stomach and small intestine. Targeting of drugs to the colon is of increasing importance for local treatment of inflammatory bowel diseases (IBD) of the colon such as ulcerative colitis and crohn's disease (CD). The prevalence of ulcerative colitis and CD ranges from 10 to 70 per 100,000 people, but recent studies in Manitoba, Canada, and Rochester, MN, have shown prevalence as high as 200 per 100,000 people.

Such inflammatory conditions are usually treated with conventional oral dosage forms might be more.

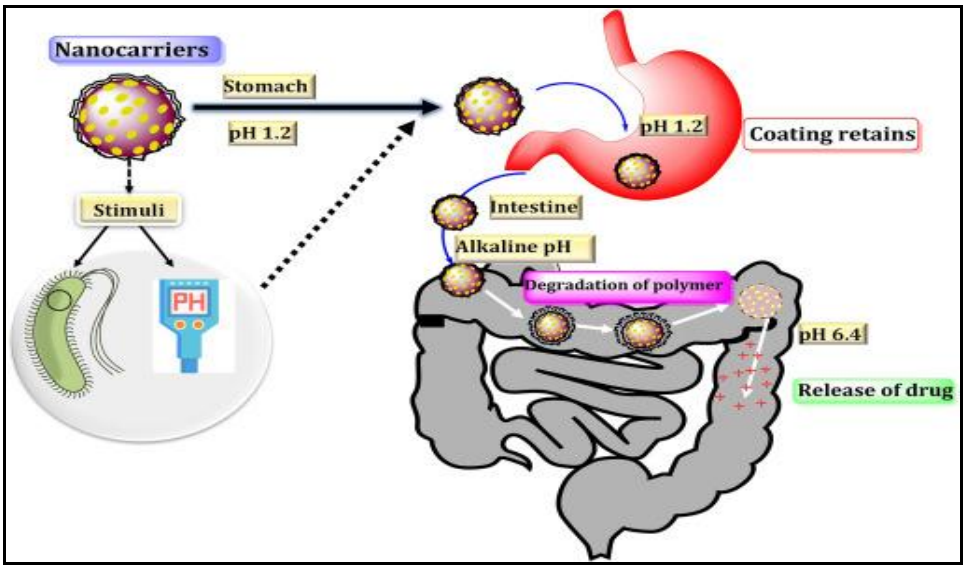

Fig. No.01: Nanocariers and Colon Targeted Drug Delivery System.

Oral route is the most convenient and preferred route but other routes for CDDS may be used. Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal. Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents.

COLONIC DISEASES

Inflammatory bowel disease (IBD)

Inflammatory bowel disease (IBD) is the communal terms for a group of idiopathic intestinal conditions include ulcerative colitis (UC) and Crohn'sdisease (CD). IBD is considered to be chronic relapsing disorder allied with uncontrolled inflammation within the gastrointestinal tract which may lead to the development of colorectal cancer later in life.

One million people in North America are reported to be affected by IBD which may be due to a dysregulated immune response to the host microflora in individuals susceptible genetically. CD and UC can be quite distinct, with different pathogenesis, inflammatory profiles, symptoms and treatment approach.

Crohn's disease

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract; it is characterized by a granulomatous inflammation affecting any part of the tract, normally form fistulae. The Crohn's disease was first described by the Crohn.

Colonic Cancer: Colonic tumors are growths arising from the inner wall of the large intestine. The large intestine may show benign tumors called polyps, and malignant tumors called cancers. Polyps are not life-threatening as they do not spread to other parts of the body and can be easily removed during colonoscopy. Although if not removed may become cancerous over period of time. Metastasis is the spread of colon cancer to distant organs, the occurrence of metastasis makes complete cure of cancer unlikely. The cancer of the colon and rectum is third major type of cancer in males and the fourth in females. The adaptation to western diets has shown an increase in incidence of colorectal cancer.

MATERIALS AND METHODS

Berberin Hydrochloride, Eudragits RS 100) (Analab Fine chemicals, Mumbai CAS No. 141433-60-5)

Materials Used

Crosspovidone, Di-calcium phosphate, Hydroxy Propyl Methyl Cellulose (HPMC) K4M, Microcrystalline cellulose MCC PH 101, Magnesium stearate, Talc.

Drug Profile

BBH is commercially used to treat duodenal and benign gastric ulcers caused by bacteria.

BBH has been found to be effective fordiabetes and obesity, partly via stimulating AMP-activated protein kinase activity. Recently, BBH has been reported as anovel cholesterol-lowering agent, and it functions through a unique mechanism distinct fromstatins.

Also Berberine hydrochloride inhibits cell proliferation and promotes apoptosis of non-small cell lung cancer via the suppression of the MMP2 and Bcl-2/Bax signaling pathways.

Chemical Formula: $C_{20}H_{18}NO_4$+

Boiling point: 145 °C

Molecular Weight: 336.4 g/mol

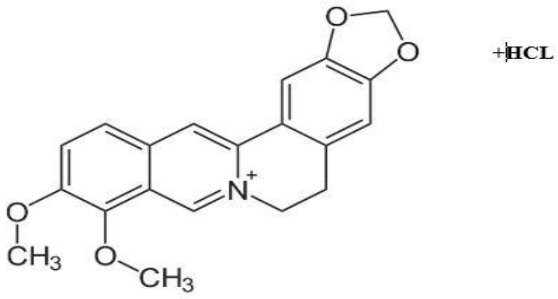

Fig. No.02: Berberin Hydrochloride.

(1,3-Benzodioxolo[5,6-a]benzo[g]quinolizinium,5,6-dihydro-9,10-dimethoxy-, hydrochloride (1:1)

Berberine Chloride is the orally bioavailable, **hydrochloride** salt form of **berberine**, a quaternary ammonium salt of an isoquinoline alkaloid and active component of various Chinese herbs, with potential antineoplastic, radiosensitizing, anti-inflammatory, anti-lipidemic and antidiabetic activities. Berberine is the principal component of many popular medicinal plants (e.g. the genus Berberis, Coptis and Hydrastis among others) with a history of thousands of years of usage in traditional medicine. The numerous pharmacological activities of berberine reported in the last two decades have been attracting high level interests both within the scientific community, clinicians and the public at large. Despite enormous amount of efforts have been placed to show its therapeutic value for inflammatory bowel diseases (IBD), however, comprehensive up-to-date review article in this field is not yet available. In this communication, literature data from in vitro and in vivo experiments were scrutinised and concisely presented to demonstrate its anti-IBD potential. Beyond the known general antioxidant and anti-inflammatory effects of berberine, IBD-specific effects

including gut epithelial barrier pathology, T cells as emerging targets, antinociceptive and other effects are discussed.

Preparation of calibration curve of Berberine chloride (2-10 µg/ml)

Preparation of standard solution of berberineAn accurately weighed quantity (10mg) of berberine was dissolved in methanol and volume was made up to 10ml with methanol in a volumetric flask. Stock solution of berberine was prepared by diluting 1 ml of this solution with methanol up to 100ml in volumetric flask to give 10 µg/ml concentratrion of berberine.

UV Spectra

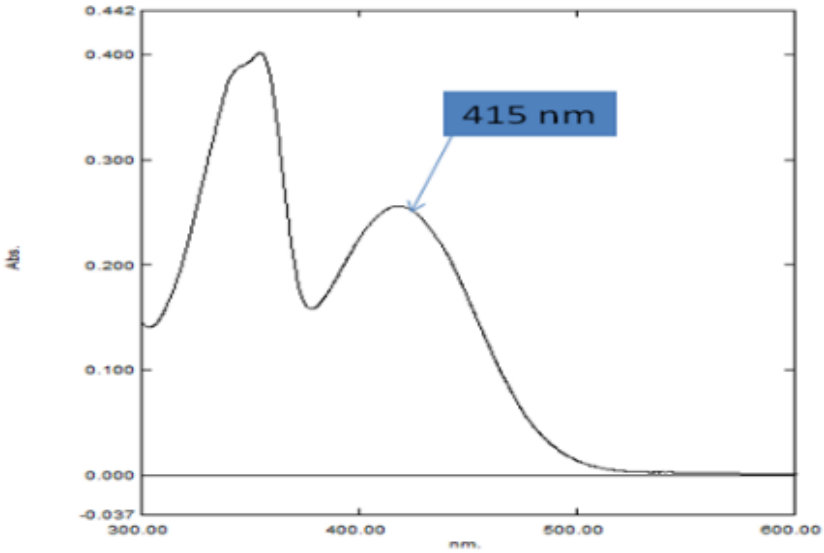

Fig. No 03: UV Spectra of BBR.

Calibration graph: UV-visible spectra of BER-H (Berberine chloride) standard solution wavelength at 415 nm

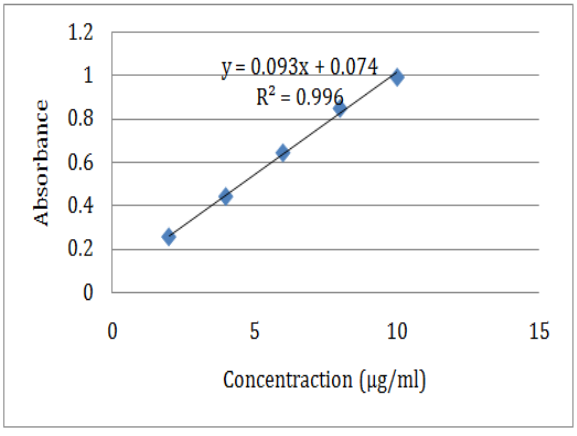

Fig. No. 04: Observed curve BBH

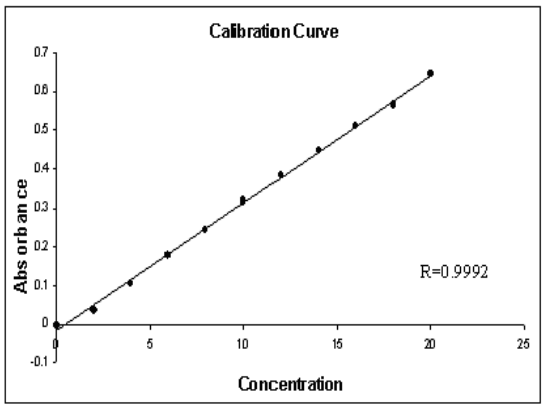

Fig. No. 05: Standard curve *BBH*

Formulation of Matrix Tablets

Table No. 01: Formulation Table of Matrix Tablet.

Sr. No	Ingredients	MT1	MT2	MT3
1	Berberine chloride	100	100	100
2	Guar Gum (GG)	175	150	125
3	Xanthan Gum (XG)	75	100	125
4	Microcrystalline Cellulose	45	45	45
5	Magnesium stearate	3	3	3
6	Talc	2	2	2
7	Total weight	400	400	400

Formulation of Core Tablet and Preparation of Compression Coated Tablets

The core tablet formulation consisted of following ingredients

Table No. 02: Core Tablet Formulation.

Sr. No	Ingredients	Core tablet
1	Berberine chloride	100
2	Microcrystalline Cellulose	20
3	Sodium starch glycholate	3
4	Magnesium stearate	0.5
5	Talc	1.5
6	Total weight	125

The above formula is for the core tablet; all the weights are in milligram.

All the ingredients from Sr.No 1 to 5 were firstly weighed and mixed in the geometric fashion. Then mixture equivalent to 100 mg of Berberine chloride (125mg) was weighed and then compressed by single station Cadmach tablet punching machine using 7 mm flat punches, optimizing the hardness and die cavity of the machine, so that the tablets will be of uniform hardness and with minimal weight variation.

Table No. 03: Compression Coating Formulations With Percent Gum content.

Sr. No.	Formulation	Drug: GG: XG
1	CT1	1:1.75:0.75
2	CT2	1:1.5:1
3	CT3	1:1.25:1.25

Table No. 04: Composition of Compression coat Formulations.

Sr. No.	Ingredients	XG1	XG2	XG3
1	Guar Gum	175	150	125
2	Xanthan Gum	75	100	125
3	Microcrystalline Cellulose	45	45	45
4	Magnesium stearate	3	3	3

5	Talc	2	2	2
6	Total weight	300	300	300

Compression Coating of Core Tablet

40% weight of Coating mixture then kept in die cavity and then core tablet was placed on it in centered position and then remaining 60% of coating mixture was added to cavity and compressed in to tablets, optimizing the hardness and die cavity of the machine. So that the tablets will be of uniform hardness and with minimal weight variation.

Evaluation of Tablet Properties

Tablets were subjected to evaluation of properties including drug content uniformity, weight variation, tablet hardness, friability, and thickness, stereomicrogrphy and in-vitro drug release studies.

Tablet hardness

The resistance of tablets to shipping or breakage under conditions of storage, transportation and handling before usage depends on its hardness. The hardness of each batch of tablet was checked by using Pfizer hardness tester. The hardness was measured in terms of kg/cm^2.[59]

Friability

Friability is the measure of tablet strength. Roche friabilator was used for testing the friability using Twenty tablets were weighed accurately and placed in the tumbling apparatus that revolves at 25 RPM dropping the tablets through distance of six inches with each revolution. After 4 min the apparatus was stopped tablets were removed and weighed, the percentage loss in weight was determined.

Tablet thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using VernierCalliper. It was determined by checking ten tablets from each formulation.

Weight variation

The weight of the tablet being made in routinely measured to ensure that a tablet contains the proper amount of drug. The USP weight variation test is done by weighing 20 tablets individually, calculating the average weight and comparing the individual weights to the average. The tablet meet the USP test if no more than 2 tablets are outside the percentage limits and if no tablets differs by more than 2 times the percentage limit.

Table No. 05: Weight variation limits.

Sr. No.	Average weight of tablet (mg)	Maximum % difference allowed
1	130 or less	10
2	130-324	7.5
3	324 or more	5

Content Uniformity

The Berberine chloride tablets were tested for their drug content uniformity. At random 20 tablets were weighed and powdered. The powder equivalent to 100 mg was weighed accurately and mixed in 100ml of phosphate buffer pH 7.4. The mixture was shaken properly. The undissolved matter was removed by filtration through Whatman No.41 filter paper. Than the serial dilution were carried out. The absorbance of the solution was measured at 415 nm. The concentration of the drug was computed from the standard curve of the Berberine chloride in phosphate buffer pH 7.4.

In Vitro drug release studies

The compression-coated tablets of **Berberine chloride** were evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. These studies were carried out using a USP XXIII dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C). The tablets were tested for drug release for 2 h in 0.1 N HCl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH 7.4-phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3 h. At the end of the time periods, two samples each of 5 ml were taken, suitably diluted and analysed for Berberinechloride nm using a double beam UV/VIS Spectrophotometer (JASCO V 530).

The drug release studies were carried out in USP dissolution rate test apparatus (apparatus 1, 100 rpm, 37°C) with slight modification. A beaker (capacity 150 ml, internal diameter 55 mm) containing 100 ml of dissolution medium was immersed in the water contained in the 1000 ml vessel, which was, in turn, in the water bath of the apparatus. The tablets were placed in the baskets of the apparatus and immersed in the dissolution added to ensure solubility of finely suspended drug particles released due to break down of the coat by the caecal enzymes. The volume was made up to 10 ml with Phosphate buffer, centrifuged and the supernatant was filtered through a bacteria-proof filter and the filtrate was analyzed for Berberine chloride content 275 nm as described above. The above study was carried out on

all the Berberine chloride tablets coated with different coat formulation CT1, CT2, and CT3 and also without caecal matter in pH 6.8 Phosphate buffer (control).

Table No. 06: Dissolution test parameter details.

Sr No.	Specification	Standard values
1	Apparatus	USP dissolution apparatus
2	Speed	100 rpm
3	Volume of media	900 ml (pH 1.2) 900 ml (pH 7.4) 900 ml (pH 6.8)
4	Dissolution Media used	pH 1.2 pH 7.4 pH 6.8 with 4% of fresh rat cecal content.
5	Stirrer	Basket type
6	Aliquot taken at each time interval of 1 hr	5 ml
7	Temperature	37± 0.5° C

RESULTS AND DISCUSSION

Pre-formulation Studies

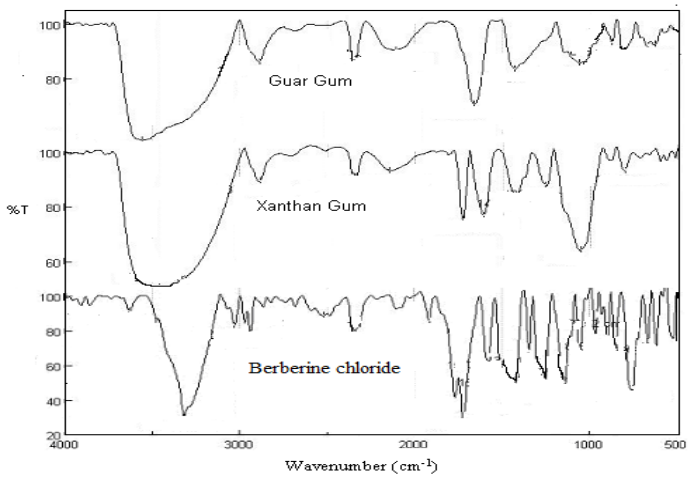

Fig. No. 06: IR spectra of Berberine chloride.

IR spectra of pure drug and the tablet powder are shown below.

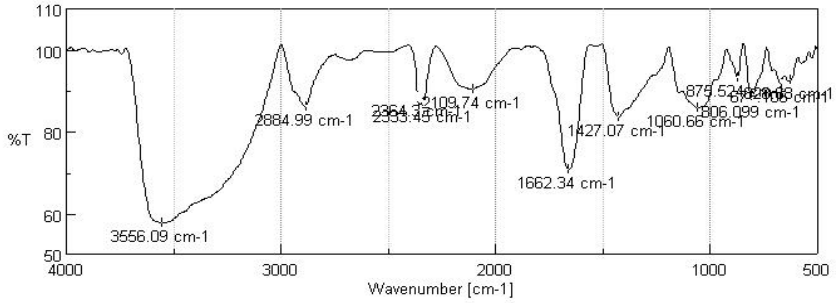

Fig. No. 07: IR spectra of pure drug.

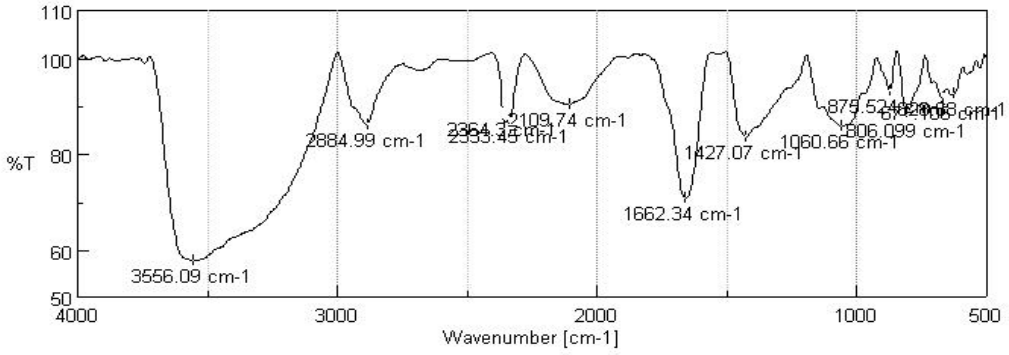

Fig No. 08: IR spectra of tablet powder.

No significant change in peak pattern in the IR spectra of pure drug and tablet powder does not indicates any interaction between pure drug, gums and excipients.

Evaluation of Tablet Properties

Table No. 07: Evaluation Parameter observation.

Formulation	Hardness ‡ Kg/cm^2	Friability ‡ %	Thickness* (mm)	Weight variation† mg.	Drug Content* %
MT1	6.8±0.2	0.37±0.2	3.85±0.02	411±9	98.04±0.05
MT2	6.8±0.3	0.35±0.3	3.91±0.03	409±11	97.13±0.06
MT3	6.7±0.3	0.41±0.4	3.87±0.00	413±8	99.40±0.04
CT1	7.2±0.2	0.43±0.3	3.93±0.04	428±9	97.33±0.03
CT2	7.4±0.2	0.41±0.4	3.86±0.02	420±11	98.21±0.04
CT3	7.4±0.3	0.43±0.2	3.95±0.04	430±9	98.03±0.02

*All values are expressed as mean ±SE, n=5

‡ All values are expressed as mean ±SE, n=6

† All values are expressed as mean ±SE, n=20

Melting Point: 204-206 ^{O}C

Assay by UV Spectrometry: 97%

Dissolution Studies

In vitro drug release studies

The percent drug released at different time periods from Berberine chloride tablets compression coated with coat formulations MT1, MT2, and MT3 in 0.1 N HCl (2 h), pH 7.4 phosphate buffer (3 h) and pH 6.8 phosphate buffer (21 h) are shown in. At the end of the experiment, all these three formulations were found to be intact retaining their coats and slight swelling of coats due to water sorption was observed. within 10 min in 0.1 N HCl and hence were not studied further. The results of the drug release studies carried out in the

presence of 4% w/v of rat caecal contents in pH 6.8 PBS are shown in At the end of 26 h of testing, tablets coated with coat formulation F1 were found to be intact. The tablets coated with coat formulation F2 were found broken at one point indicating commencement of the disintegration of the coat whereas the coat formulation F3 was completely disintegrated.

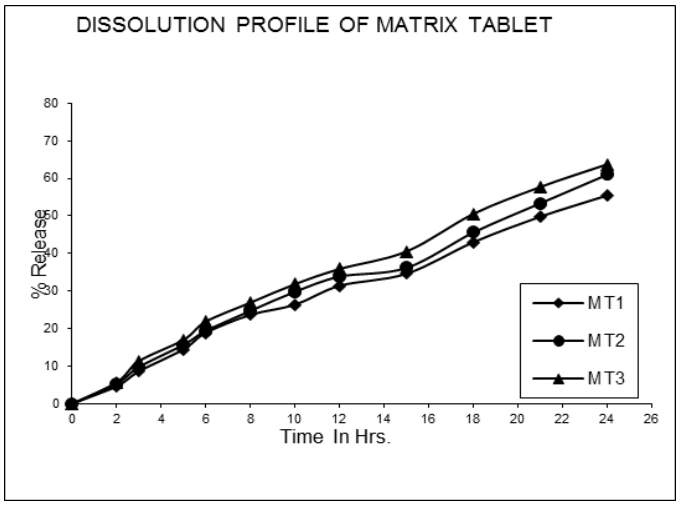

Fig. No. 09: Dissolution profile of Matrix Tablet.

The percent drug released at different time periods from Berberine chloride tablets compression coated with coat formulations CT1, CT2, and CT3 in 0.1 N HCl (2 h), pH 7.4 phosphate buffer (3 h) and pH 6.8 phosphate buffer (21 h) are shown in. At the end of the experiment, all these three formulations were found to be intact retaining their coats and slight swelling of coats due to water sorption was observed. However, tablets coated with coat formulation F4 were found broken within 10 min in 0.1 N HCl and hence were not studied further. The results of the drug release studies carried out in the presence of 4% w/v of rat caecal contents in pH 6.8 PBS are shown.

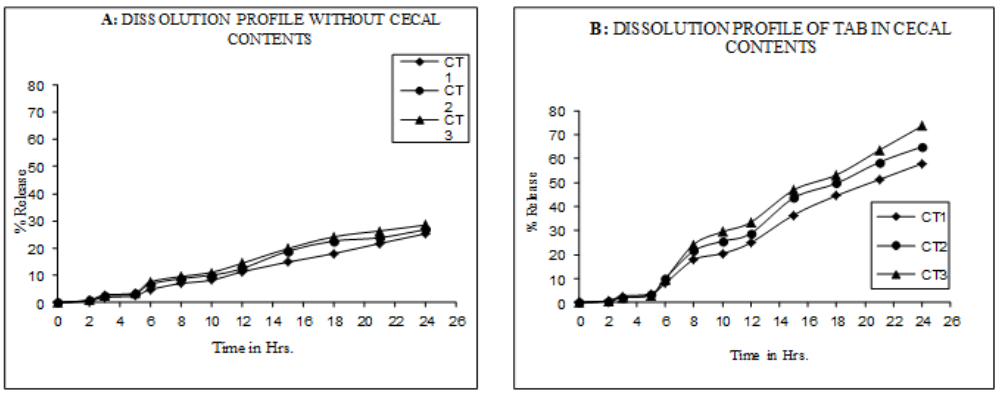

Fig. No 10: A: Dissolution Profile without cecal content, B: Dissolution Profile cecal content.

Gaur gum and Xanthan gum combinations

The drug release pattern for the Guar gum and Xanthan gum combination matrices were studied by same method as previous. The % cumulative drug release obtained was as follows. From the graph it was observed that the drug release from the GG: XG (15:15) is much retarded as compared to the GG: XG (10:20) and GG: XG (20:10). The effect may be because of higher concentration of Xanthan gum in the former. During first 5 h of dissolution drug release was reduced in GG: XG (15:15) to 16% from the 29-30% in the other combinations. This can be explained on the basis that on exposing the tablets to the dissolution media, the gums with synergistic gelling properties form a viscous gel that slows down the further seepage of dissolution fluid into the tablet. The initial delay in drug release can also be attributed to the time taken for the glassy to rubbery transition by the gum combination the drug present on the surface of the tablet accounts for the initial release seen.

CONCLUSION

The present study shows targeted delivery of BBH with respective tablet formulation. Natural gums gaur gum and xanthan gum used to increase retardation time. The drug release from the GG: XG (15:15) is much retarded as compared to other trial batches.

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