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Research Article

Formulation and Evaluation of Microbially- triggered tablets of Valdecoxib

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Abstract
The objective of present study was to develop colon targeted drug delivery using bacterially triggered approach through oral route. Valdecoxib (COX-2 inhibitor) was chosen as a model drug in order to target it to colon which may prove useful in inflammatory bowel disease and related disorders. Matrix tablets of Valdecoxib were prepared by wet granulation technique utilizing different ratio of Guar gum and Sodium starch glycholate. The prepared matrix tablets were evaluated for uniformity of weight, uniformity of content, hardness and *in vitro* dissolution study in simulated gastric and intestinal fluid (Phosphate Buffer pH-1.2, pH-6.8 and pH-7.4), followed by Dissolution study in bio-relevant dissolution media Phosphate Buffer (pH-6.8) containing rat caecal content. The results revealed that the formulated batch had released lesser quantity of drug at pH 1.2 and pH 7.4 in 2 hors whereas in biorelevent dissolution media containing rat caecal content it released significantly higher amount of drug which was also significantly higher than the dissolution media of same pH without caecal content (microflora) and it was concluded that guar gum can be used as a potential carrier for targeting drugs to colon.

Keywords: Valdecoxib, bacterially triggered, matrix tablets, colon targetting

Introduction:

Oral drug delivery system is the most commonly used route for drug delivery due to its ease of administration, better patient compliance, and flexibility in design and development of formulation. Recently drug delivery to colon has attracted a lot of attention of the scientist working on oral drug delivery system which is mainly due to the fact that colon is a site where both local and systemic drug delivery can take place [1]. A number of diseases of colon such as colorectal cancer, irritable bowel syndrome, and inflammatory bowel disease can be treated more effectively if drugs were targeted directly to colon. The development of new therapeutic agents for the treatment of colonic diseases has provided a boost to colonic delivery system in order to maximize their therapeutic efficacy.

Most of the drugs when taken through oral route release their content in stomach and small intestine. Drugs are also metabolized through phenomenon called as first pass metabolism. So drugs are targeted particularly to colon to prevent first pass metabolism and release of drugs in stomach and small intestine. Site specific drug delivery to colon allows oral administration of such drugs which are normally inactivated in upper part of gastrointestinal tract and has provided a new tool to the scientist for drug delivery of vaccines, insulin and growth hormones etc which were otherwise been given through pareneteral route. [2, 3]

Valdecoxib, a nonsteroidal anti-inflammatory drug (NSAID) that exhibits anti-inflammatory, analgesic and antipyretic properties was chosen as a model drug due to its high first pass metabolism. It undergoes both P450 and non-P450 dependent (glucuronidation) metabolism. The mechanism of action is believed to be due to inhibition of Prostaglandin synthesis primarily through inhibition of cyclooxygenase-2 (COX-2).

Both anaerobic and aerobic microorganisms inhabit the human gastrointestinal tract [2, 4]. The microflora of the small intestine is mainly aerobic, whereas in large intestine, it is mainly anaerobic and about 400 bacterial species have been reported in colon. Most bacteria inhabit the proximal part of large intestine, where energy source are greatest [2]. Carbohydrates are the main source of nourishment for bacteria in colon and based on this fact a colon targeted drug delivery using microbial triggered approach was developed. The carbohydrates are metabolized by the enzyme glycosidase and polysaccaridase and if the drug is incorporated along with these natural substances, they will release drug particularly into colon because they are preferentially degraded in the colon by colonic bacteria.

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TABLE-1 Formula for colon targeted drug delivery using microbially triggered approach

Ingredients (mg)	V/GS:50	V/GS:41	V/GS:32	V/GS:23	V/GS:14	V/GS3.5/1.5
Valdecoxib (drug)	20	20	20	20	20	20
Guar gum	174	138	102	66	30	120
Sodium starch glycolate (SSG)	-	36	72	108	144	54
Talc	4	4	4	4	4	4
Magnesium sterate	2	2	2	2	2	2

TABLE-2 Evaluation of prepared tablets of various Batches

Batch No	Average Weight	Hardness	Drug Content	Drug Content after 1 month
V/GS:50	206.5	7.9 ± 0.5	20.2 ± 0.67	20.1 ± 0.73
V/GS:41	210.6	7.7 ± 0.9	19.9 ± 0.07	19.9 ± 0.87
V/GS:32	204.1	7.8 ± 0.6	20.1 ± 0.11	20.9 ± 0.31
V/GS:23	202.7	7.6 ± 0.7	20.2 ± 0.09	20.2 ± 0.07
V/GS:14	204.7	7.4 ± 0.8	20.3 ± 0.45	20.2 ± 0.14

A number of substances has been reported to be used for colon targeting such as Amylose [5], Pectin [4, 6], Cross linked guar gum[7], and Chitosan [8, 9]. Most of these polymers are hydrophilic in nature, and after absorbing water they swell and form a viscous gel layer around the dosage form resulting into delayed/ sustained drug release. Drug will be preferentially released in the colon, the site where polymer has been degraded by the microflora of colon. Guar gum derived from the seeds of Cyamposis tetragonolobus is a naturally occurring galactomanan polysaccharide. It contains about 80% galactomanan, 12% water, 5% protein, 2% acid insoluble ash, 0.7%ash and 0.7% fat. Guar gum hydrates and swells in water forming viscous colloids dispersion solutions [10]. Guar gum is used to deliver drug to the colon due to its drug release retarding property and susceptibility to microbial degradation in large intestine [11]. Xanthan gum, guar gum, chitosan and Eudragit E-100 can be effectively used as binder to target drugs to colon effectively after coating the formulations with enteric coating polymers such as Eudragit L-100 [12, 13. 14]. Guar gum has also been used in the form of compression coat over tablets for colon targeting [13]. The present work deals with preparation and evaluation of colon specific drug delivery of Valdecoxib using Guar gum as a natural polymer.

Material and Method:

Valdecoxib was obtained as gift sample from Sytopic Labs Ltd. (New Delhi), whereas, Guar gum and Sodium starch glycholate were generously gifted by Dabur India Ltd and Vardhman Healthcare Ltd. (Mullana, India) respectively. Other materials used in study such as microcrystalline cellulose, Starch, Magnesium stearate, Talc etc were of suitable analytical grade.

Preparation of Valdecoxib matrix tablets:

Matrix tablets of Valdecoxib were prepared by wet granulation technique. Valdecoxib was mixed with guar gum and sodium starch glycholate in different ratios as shown in table 1. Microcrystalline cellulose was taken as diluent utilizing 10% starch paste as binder. A mixture of talc and magnesium stearate (2:1 ratio) was used as

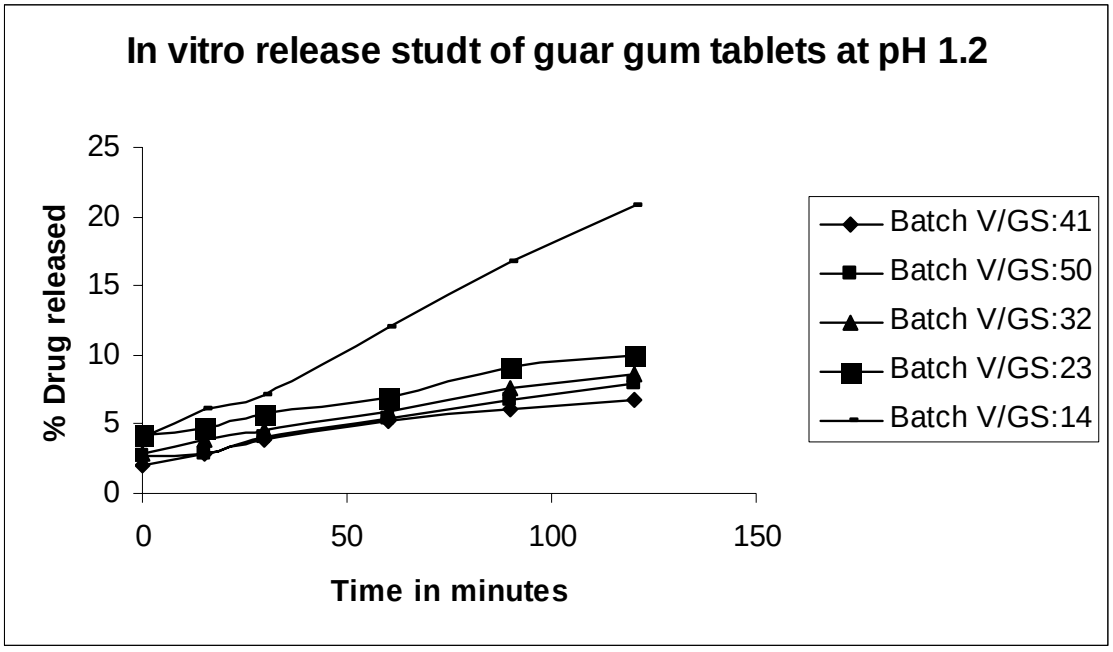

Fig 1: In-vitro release study of guar gum tablets at pH 1.2

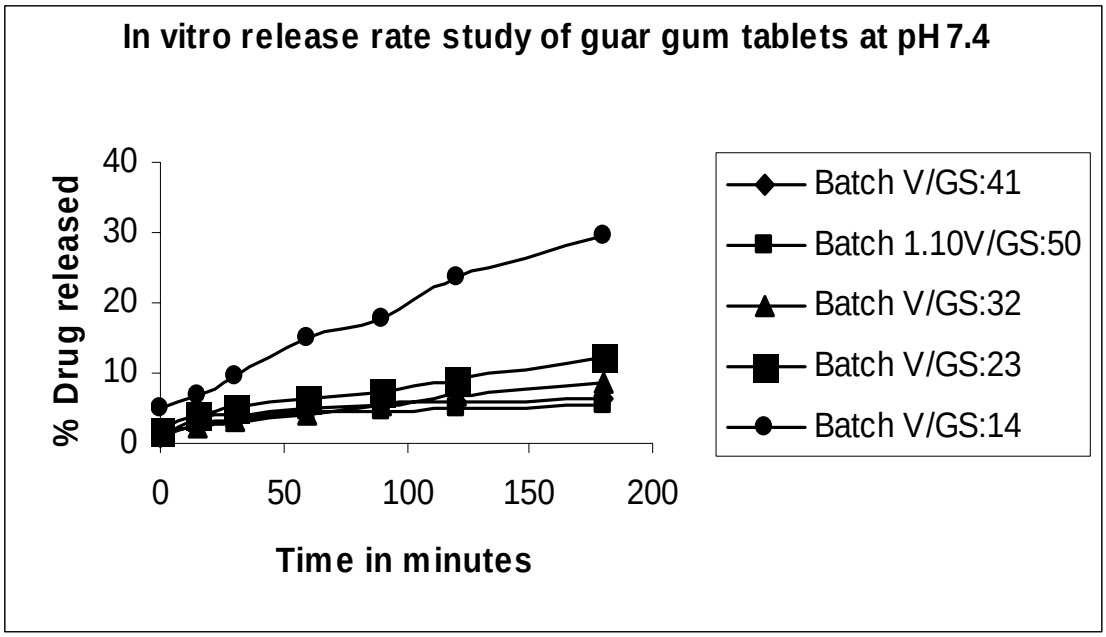

Fig 2: In-vitro release rate study of guar gum tablets at pH 7.4

lubricant. Five formulations were prepared having different amount of guar gum and sodium starch glycholate and coded as V/GS: 50, V/GS: 41, V/GS: 32, V/GS: 23, V/GS: 14. In all the formulations guar gum was first powdered using mortar-pestle and sieved (<250µm) separately. Afterwards guar gum was mixed with Valdecoxib (<150µm), microcrystalline cellulose (<250µm) and sodium starch glycholate (<250µm). Mixing was carried out in double cone blender for 30 minutes. Amount of drug and lubricant was kept constant in each formulation. The mixed powders were then granulated using 10%starch paste. The wet mass was passed through mesh no (1680µm) and the granules were dried at 50^0C for 2 hours. The dried granules were passed through mesh no (1190µm) and then lubricated with mixture of talc and magnesium stearate (2:1 ratio). The obtained granules were then compressed using 8 mm punch on R&D tablet punching machine adjusting the tablet weight to 200mg so that each tablet contains 20mg of Valdecoxib. Matrix tablets of each composition were then evaluated for different parameters such as hardness, uniformity of weight, uniformity of content, In vitro dissolution study, and stability studies

Hardness of tablets:

Matrix tablets of Valdecoxib were evaluated for their hardness using Monsanto hardness tester. The tablet hardness/ crushing strength was measured in kg/cm^2 and the results are shown in table-2.

Uniformity of weight:

Prepared tablets were evaluated for uniformity of weight. Twenty tablets were weighed individually and the average weight was calculated. From the average weight of tablets the standard deviation and individual deviations were determined and the results are shown in table-2.

Uniformity of content:

Twenty tablets were weighed and powdered. The powdered tablet equivalent to 20 mg of Valdecoxib was taken and kept in 100ml of distilled water in 250ml flask

TABLE-3 Percent Drug release from different batches at pH 1.2

S No	Time in minutes	Batch V/GS:41	Batch V/GS:50	Batch V/GS:32	Batch V/GS:23	Batch V/GS:14
1	0	2.08	2.67	2.93	4.20	3.99
2	15	2.94	2.94	3.87	4.69	6.14
3	30	3.87	4.13	4.48	5.80	7.12
4	60	5.16	5.33	5.88	6.87	11.97
5	90	6.01	6.77	7.59	9.16	16.80
6	120	6.74	7.97	8.66	9.99	20.78

TABLE-4 Percent Drug release from different batches at pH 7.4

S. No	Time in minutes	Batch V/GS:41	Batch V/GS:50	Batch V/GS:32	Batch V/GS:23	Batch V/GS:14
1	0	1.06	1.10	1.70	1.70	4.88
2	15	3.66	2.73	2.43	4.09	6.94
3	30	4.01	3.11	3.36	5.16	9.50
4	60	5.07	4.38	3.96	6.18	14.79
5	90	5.50	4.69	5.46	7.38	17.59
6	120	5.85	5.07	6.78	9.05	23.59
7	180	6.19	5.29	8.65	12.41	29.45

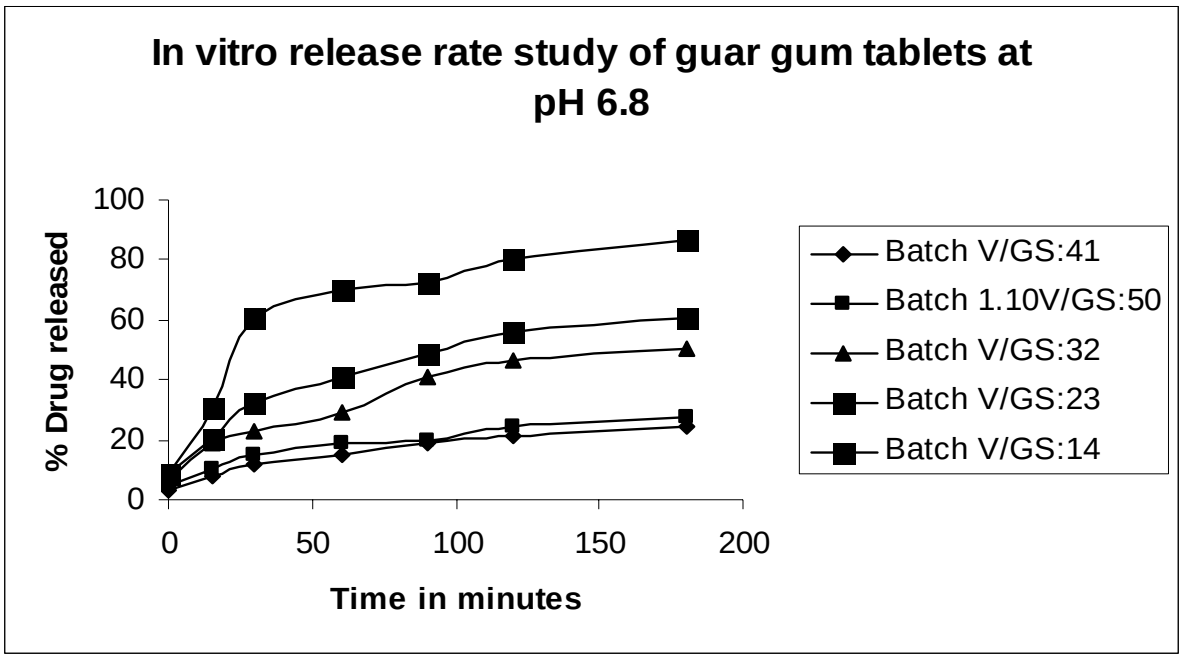

Fig 3: Invitro release rate study of guar gum tablets at pH 6.8

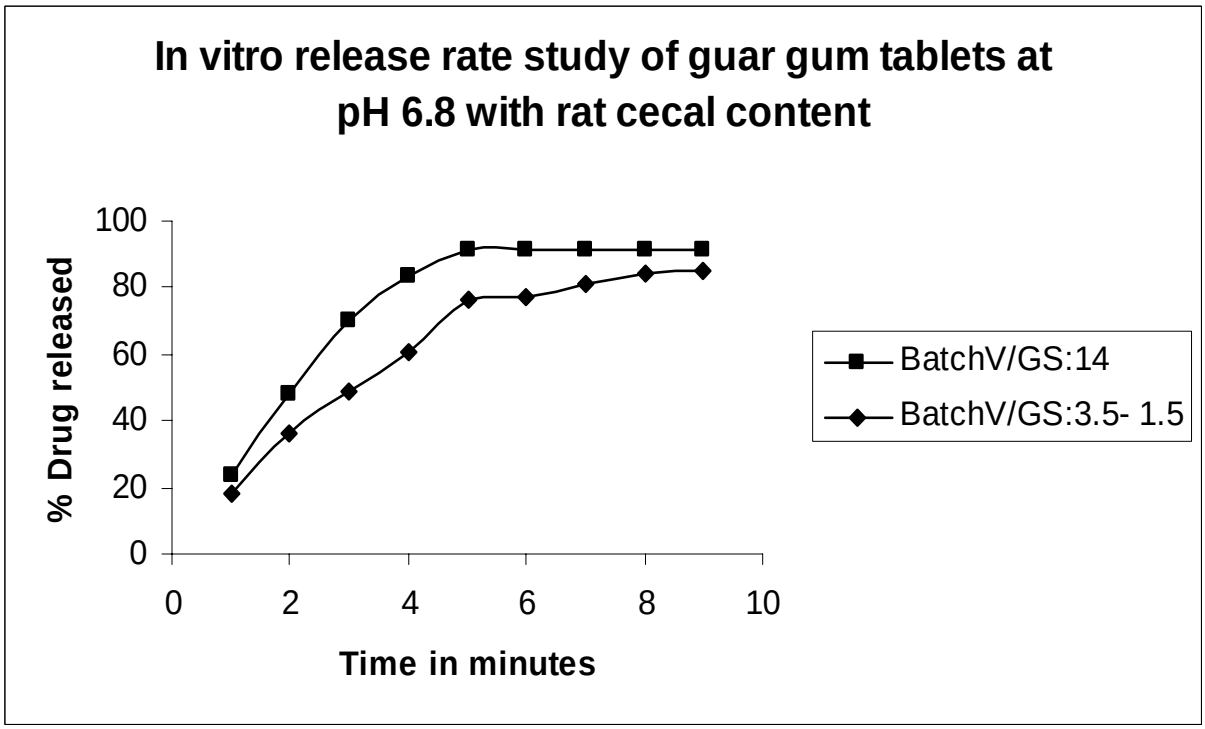

Fig 4: Invitro release rate study of guar gum tablets at pH 6.8 wih art cacal content

and was placed on the flask shaker for 24 hours and further after 12 hours standing it was filtered. 10 ml of this filtrate was diluted to 100ml with distilled water and was analyzed at 241nm using UV visible spectrophotometer and total drug content was calculated and the results are shown in table-2.

In Vitro Drug release studies in Phosphate Saline Buffer (pH 1.2 and pH 7.4):

Valdecoxib guar gum matrix tablets were subjected to in vitro drug release studies in simulated gastric and intestinal media to study amount of drug release in particular media. Drug release studies were carried out using USP dissolution rate test apparatus (Apparatus 1, 100rpm, 37±0.7ºC). The tablets were studied in pH 1.2 buffer (900ml) for 2 hrs as the average gastric emptying time is nearly 2hrs.Then the tablets were tested in pH 7.4 buffer (900ml) for 3 hrs as the average small intestinal transit time is nearly 3hrs.Two samples each of 1ml were

TABLE-5 Percent Drug release from different batches at pH 6.8

S. No	Time in minutes	Batch V/GS:41	Batch V/GS:50	Batch V/GS:32	Batch V/GS:23	Batch V/GS:14
1	0	3.42	4.77	6.16	8.91	8.73
2	15	7.94	10.23	18.57	20.65	30.95
3	30	11.92	14.85	23.05	32.01	60.56
4	60	14.86	18.66	29.46	41.30	70.35
5	90	19.02	19.81	40.93	48.73	72.48
6	120	21.02	24.54	46.66	55.75	80.45
7	180	24.77	27.71	50.65	60.69	86.39

taken and mixed with 1 ml of methanol to ensure the solubility of finely suspended particles of Valdecoxib. Afterwards samples were diluted with respected dissolution fluid to make up to 10 ml. Then the samples were analyzed at 241nm using double beam spectrophotometer to find out the amount of Valdecoxib released from matrix tablets.

TABLE-6 Percent Drug release from different batches pH 6.8 in rat cecal content

S No.	Time	BatchV/GS:3.5- 1.5	BatchV/GS:14
1	0 min	18.14	23.54
2	15 min	36.26	48.36
3	30 min	49.07	70.47
4	60 min	60.74	83.13
5	2 hrs	76.57	91.28
6	4 hrs	77.43	91.30
7	8 hrs	81.13	91.40
8	16 hrs	84.61	91.45
9	24 hrs	84.98	91.55

Drug release studies in presence of rat caecal content:

As the guar gum which was used as a polymer to make formulations was susceptible to microbes present in the colon therefore dissolution rate studies were also performed using rat caecal content because of similarity with human colonic microflora to simulate the microbial environment of colon. The use of rat caecal content was approved by CPCSEA, Department of Pharmaceutical Sciences, GJUS&T, Hisar, Haryana, India.

Albino rats which were maintained on normal diet were used and provided with guar gum aqueous dispersion (1ml of 2%w/v dispersion) for 6-7 days using a Teflon tube intubated directly into stomach of rat and was removed after feeding. Thirty minutes before the commencement of study four rats were killed, their abdomen were opened, caecum isolated, ligated from both ends, cut loose and transferred immediately into phosphate saline buffer (pH 6.8) bubbled with CO_2 gas. Afterwards caecal bags were opened and their content were weighed and diluted with phosphate saline buffer to obtain 4%w/v rat caecal content which was used for further studies. As the caecum is anaerobic in nature, the experiments were performed under the environment of CO_2 gas.

The drug release study was carried out using the same USP dissolution rate test apparatus using 85 ml of Phosphate saline buffer(pH 6.8) having 4%w/v rat caecal content in 150 ml of beaker which in turn was placed in 1000ml vessel having water in it and placed inside the water bath. The formulated tablets were placed inside the basket of apparatus and immersed in the dissolution medium i.e. phosphate saline buffer (pH 6.8) having rat caecal content in it. The experiment was carried out for 24 hrs with continuous supply of CO_2 to provide anaerobic environment. At different time interval 1ml of sample was withdrawn without a prefilter and was replaced with the same dissolution medium freshly bubbled with CO_2 gas to maintain the sink condition. Afterwards each withdrawn samples was mixed with 1ml of methanol to ensure solubility of suspended Valdecoxib particles and also diluted with phosphate saline buffer pH6.8 to make volume up to 10ml. Then samples were centrifuged and supernatant was removed using bacteria proof filters (G5) and the filtrates were analyzed for Valdecoxib at 241nm using Double beam spectrophotometer.

The same experiment was repeated under same conditions using same phosphate saline buffer but without rat caecal content (control) to evaluate drug release in the absence of bacterial enzymes for 24 hrs. The results obtained were compared with the previous once.

Stability study:

Stability study was carried out on matrix tablets of Valdecoxib for determining physical appearance, drug content and drug release characteristics after storing tablets at 40^0C and 75% relative humidity for one month.

Result and Discussion:

The prepared tablets were found to be well within the pharmacopoeial limit in weight variation test i.e. (±7.5%). Moreover crushing strength was found to be between 7-8 kg/cm^2 and the content uniformity study revealed that percentage of drug in the tablet was well within the pharmacopoeial limit.

It is clearly depicted from the in vitro dissolution study of guar gum tablets at pH 1.2 that different batch of bacterially triggered tablets swells slightly and remained in the basket for up to 2 hours. As shown in the table maximum percentage of drug dissolved was observed with the batch number V/GS: 1:4 (20.78%) and whereas in all other batches percentage drug dissolution increases accordingly with increase of SSG (sodium starch glycholate) On the other hand the in vitro drug dissolution study in Phosphate buffer (pH 7.4) for 3 hours, the percentage of drug dissolved with batch V/GS 1:4 was 29.45% whereas batch V/GS: 5:0 shows 6.19% of drug dissolved due to surface drug dissolution.

Likewise in vitro dissolution study in pH 6.8 for 3 hours, the maximum percentage drug dissolved was observed with the batch V/GS: 1:4 that was 86.39% due to burst release effect of SSG and whereas batch V/GS: 3:2 gives 50.65% and V/GS: 2:3 gives 60.69% drug release. Because it is clearly observed from release profile that

optimized batch is present in between batch V/GS: 3:2 and V/GS: 1:4 so percentage of drug dissolved in anaerobic bacterial solution at pH 6.8 was studied using new formulated batch V/GS: 3.5:1.5. It is observed from study that V/GS: 3.5:1.5 give uniform release of drug like 49.07% in 30 minutes, 76.57% in 2 hours and 84.98% in 24 hours however batch V/GS:1:4 gives 70.47% in thirty minutes, 91.28% in 2 hours and 91.55% in 24 hours which is clearly indicated that maximum drug has been dissolved only in 2 hours, representing the excessive loss of drug and reduced patient compliance to maintain the therapeutic range for the treatment of Chron's disease and Arthritis. So this formulation having better targeting to colon proves be a better tool in improving the therapeutic benefits of NSIADS and has tremendous potential to provide relief from peptic ulcers along with IBD and Arthritis especially in geriatric patients.

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