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Research Article

FORMULATION DEVELOPMENT AND CHARACTRIZATION OF POLYSACCHARIDES MATRICES FOR MICROBIALLY TRIGGERED COLONIC DELIVERY OF MEBEVERINE HCL

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Abstract

The objective of the present study was to develop and evaluate microbially triggered colon specific matrices of mebeverine Hcl using various polysaccharides like guar gum (GG), locust bean gum (LBG), psyllium husk (PH) and also xanthan gum (XG) to achieve higher drug release control. The tablets were prepared by both direct compression and wet granulation method. Pre-formulation and micromeritic studies of the drug, polymer & physical mixture were carried out. The matrix tablets were evaluated for their physico-chemical properties, *in-vitro* release (in presence and absence of rat caecal contents) and stability studies. The results of pre-formulation studies were in accordance with reported literature values. The prepared tablets were found to be uniform with respect to thickness (5.53 to 6.03 mm) and hardness (5.7 to 6.9 kg/cm^2). The friability (0.41 to 0.95 %) and weight variation (1.04-1.66%) of different batch of tablets were found within prescribed limits. Drug content (96.01 to 99.89 %) was found uniform within the batches of different tablets. Swelling studies indicated that, matrix tablets prepared with XG alone (X4) and in combination with PH (PX4) swelled more as compared to those prepared using GG, LBG and PH. The order of swelling was XG>PH>GG>LBG for tablets prepared with single polymer and (XG+PH)> (XG+GG)> (XG+LBG) with combinations. Release profiles indicated that, increase in the polymer concentration has drastically retarded the release of mebeverine Hcl. Optimum release over a period of 24 hrs was obtained with drug polymer ratio of 1:1.5. Among the various polymers studied, XG gave better controlled release with alone (X4) and in combination with PH (PX4). *In vitro* release studies carried out in presence of rat caecal contents demonstrated the susceptibility of the polysaccharides towards colonic microflora and thereby triggering the drug release except XG. The mechanism of drug release was Non-Fickian diffusion controlled first order kinetics for optimized matrix tablets of GG (G4), LBG (L4) and XG+PH (PX4) where as for XG (X4) it followed Highuchi model. Stability studies indicated that the prepared tablets fairly remained stable during the one month stability period. FT-IR and DSC studies revealed the integrity of the drug in the formulations. Thus, the polysaccharide matrices can be efficiently prepared for the colonic delivery of mebeverine Hcl with the desired release profiles.

Keywords: Irritable bowel syndrome; Mebeverine Hcl; Colon specific; Polysaccharides; Rat caecal contents; *In- vitro* release;

Introduction

Irritable bowel syndrome: Irritable bowel syndrome (IBS) is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation and diarrhea. IBS causes a great deal of discomfort and distress, but it

does not permanently harm the intestines and does not lead to a serious disease, such as cancer. Most people can control their symptoms with diet, stress management and prescribed medications. For some people, however, IBS can be disabling. They may be unable to work, attend social events, or even travel short distances.

As many as 20 percent of the adult population, or one in five Americans, have symptoms of IBS, making it one of the most common disorders diagnosed by doctors. It occurs more often in women that in men, and it begins before the age of 35 in about 50 percent of people.[1]

Mebeverine Hcl is a musculotropic antispasmodic drug without atropic side effect, whose major therapeutic role is in the treatment of irritable bowel syndrome. Mebeverine Hcl directly act on the gut muscles at the cellular level to relax them.[2]

It is having a short biological half life of 2.5hrs, plasma protein binding 75% and rapidly absorbed after oral administration with peak plasma concentration occurring in 1-3hrs.[3] However, mebeverine Hcl suffers from extensive first pass metabolism in the gut wall and liver. High plasma concentration of veratric acid (one of the main inactive metabolites of mebeverine Hcl) in addition to negligible amounts of the parent drug were observed in plasma 20-30 minutes after oral administration.[4] Hence, mebeverine Hcl has been selected as a model drug as it fulfills the required pharmacokinetic and physicochemical properties for the controlled delivery.

Colon specific drug delivery system:

The advantages and necessity of colon targeting to provide more effective therapy for colon related disease, such as irritable bowel syndrome, colon cancer[5] and inflammatory bowel disease (IBD), including Crohn's disease and ulcerative colitis[6], have been well recognized. The ability to deliver drugs to the human colon in a specific manner has become feasible over the years. Targeting drugs to the colon makes it possible to achieve local or systemic drug delivery to this site. To deliver the compounds in a non-degraded form to the lower part of the gastrointestinal tract, they must first of all pass through the stomach, the upper part of the intestine and must use the characteristics of the colon to specifically release the drugs in this part of the digestive tract. The colon as a site for drug delivery, offers distinct advantages on account of a near neutral pH, a much longer transit time, relatively low proteolytic enzyme activity and a much greater responsiveness to absorption enhancer[7] These criteria favor this distal part of the gastrointestinal tract (GIT) as a site for the delivery of various drug molecules, including proteins and peptides.[8] colon-specific delivery system should prevent the release of the drug in the upper part of GIT

and require a triggering mechanism to affect an abrupt release on reaching the colon. In the past, various primary approaches for colon-specific delivery, such as pro-drugs, pH sensitive polymers, timed release delivery systems and microbially degraded delivery system, have achieved limited success. The majority of these systems, developed during the past decade, were based on pH and time dependent mechanisms with limited *in-vivo* evaluation. Minor variation in pH between the small intestine and the colon makes the pH dependent systems less specific, in terms of targeted release in the colon. Time-dependent formulations predominantly depend upon on the transit time of the delivery system in the GIT. A major limitation with these systems is that *in vivo* variation of the small intestinal transit time may lead to release of the bioactive in the small intestine or terminal part of the colon. The patho physiological state of an individual will have a significant impact on the performance of these time-dependent systems. Patients with irritable bowel syndrome[9] and ulcerative colitis[10] exhibited accelerated transit through different regions of the colon.

Among the different approaches available to achieve targeted drug release to the colon, the use of especially biodegradable polymers holds great promise. Natural polysaccharides, however, fall under the category of "GRAS" (Generally regarded as safe), thus resolving the general problems associated with safety.[11]

This family of natural polymers has great appeal to drug delivery as it is comprised of polymers with a large number of derivatizable groups, a wide range of molecular weights, varying chemical compositions and for the most part, low toxicity and biodegradability yet high stability. The most favorable property of these materials is their approval as pharmaceutical excipients. Polysaccharidases are bacterial enzymes that are available in sufficient quantity to be exploited in colon targeting. Bacterial sources of polysaccharides as well as detailed treaties of the enzymatic flora of the colonic region has been reviewed, along with a wide range of the polysaccharides which can be used solely for the purpose of colon-specific drug delivery. [12]

Xanthan gum is a high molecular weight polysaccharide gum produced by pure-

culture aerobic fermentation with gram-negative bacterium, *Xanthomonas campestris*. It contains D-glucose and D-mannose as the dominant hexo units, along with D-glucuronic acid. It is used in oral and topical pharmaceutical formulations as a suspending, thickening and stabilizing agent.[13]

Guar gum is a natural nonionic polysaccharide derived from the seeds of Cyamopsis tetragonolobus (Family: Leguminosae). It consists of a linear chain of (1-4)-beta-D-mannopyranosyl units with alpha-D-galactopyranosyl units attached by linkages. It is used in pharmaceutical preparation in the

form of binder and disintegrating, suspending, thickening and stabilizing agent.[14] Guar gum has recently been highlighted as an inexpensive and flexible carrier for oral extended release drug delivery. Guar gum is particularly useful for colon delivery because it can be degraded by specific enzymes in this region of the gastrointestinal tract. The gum protect the drug while in the stomach and small intestine environment and delivers the drug to the colon where it undergoes assimilation by specific microorganisms or degradation by the enzymes excreted by these microorganism.[15]

Locust bean gum is a neutral polysaccharide having a molecular weight of 3, 10,000 derived from the endosperm of the seed of the Ceratonia Sliqua linn (Fam: Leguminosae). The locust bean contains about 88% D-galacto-D-mannoglycan, 4% of pentan, 6% of protein, 1% of cellulose and 1% ash. Locust bean gum was used to produce matrix tablets with and without the cross-linker glutaraldehyde that showed similar drug release profile for different model drugs as guar gum and scleroglucan. In another study sustained release tablets could be obtained for minimatrix systems made from locust bean gum. A commercially available tablet system (TIMERx®) developed by penwest Pharmaceuticals Company consisting of locust bean gum and Xanthan gum showed both *in vitro* and *in vivo* controlled release potential.[15]

Psyllium mucilage is obtained from the seed coat of *Plantago ovata* by milling the outer layer of the seeds. It has been evaluated for its tablet binding properties, but also to form hydrogels through radiation-induced cross-linking for controlled release of 5- flurouracil as model drug. Psyllium and methacrylamide based hydrogels were prepared by using *N, N`*-methyllenebiscrylamide as cross-linker, which were then loaded with insulin. The cross-linked hydrogels showed controlled release of the active ingredient by means of non-Fickian diffusion of the drug through polymer chain relaxation during swelling. Psyllium husk was used in combination with other excipients such as hydroxypropyl methylcellulose to prepare novel sustained release, swellable and bioadhesive gastro retentive drug delivery system for ofloxacin.[15] Very few works have been reported on utilization of psyllium husk as a release retarding material. Along with its ability to control the drug release, it is also used to over come the constipation observed in the IBS[15]. Hence in the present study, psyllium has been selected as a matrix forming agent/release modifier in the preparation of matrix tablets of mebeverine Hcl.

Thus, the present investigation is aimed at using the inexpensive, naturally occurring and abundantly available polysaccharides for colon-targeted drug delivery. An attempt has been made to formulate a dosage that:

1. Retards drug release in the tracts of the

upper GIT.

2. Consist of biodegradable polysaccharides as the main constituents.
3. Is degradable by a wide range of microbial species.
4. Shows rapid drug release in the tracts of the colon due to the presence of a high concentration of degradable polysaccharides in the tablet.
5. Could be formulated using the usual tableting techniques.[1] .

Material and method

Table 1: Material

Sl. No	Chemicals	Supplier / Manufacturer
1.	Mebeverine HCL BP	Gift sample, Rentus Pharma Pvt. Ltd., Andhrapradesh.
2.	Guar gum	Gift sample, Crystal colloid, Mumbai.
3.	Xanthan gum	Gift sample, Crystal colloid, Mumbai.
4.	Locust bean gum	Gift sample, Crystal colloid, Mumbai.
5.	Psyllium husk	Gift sample, Crystal colloid,Mumbai.
6.	Starch (soluble)	S.D. Fine Chemicals Pvt limited, Mumbai.
7.	Microcrystalline Cellulose	S.D. Fine Chemicals Pvt limited, Mumbai.
8.	Talc	S.D. Fine Chemicals Pvt limited, Mumbai.
9.	Magnesium stearate	S.D. Fine Chemicals Pvt limited, Mumbai.
10.	Sodium chloride	S.D. Fine Chemicals Pvt limited, Mumbai.
11.	Potassium di-hydrogen orthophosphate	S.D. Fine Chemicals Pvt limited, Mumbai.
12.	Carbon dioxide cylinder and regulator kit	Desai Pharm Agencies, Raichur.

Table 2: Animals

Sl.No.	Type of Animal	Weight (gms)	Source
1.	Swiss albino rats	140 to 200	Sri Venkateshwara enterprises, Bangalore

Table 3: Equipments

Sl. No	Name of the Equipment	Supplier / Manufacturer
1.	Digital balance (AX-200)	Shimadzu Corporation, Japan
2.	Electronic balance (FEJ-300)	Oriental Balance Manufacturing Company, Varanasi.
3.	UV-Visible spectrophotometer (1700)	Shimadzu Corporation, Japan.
4.	Hot air oven	Servewell Instruments and Equipments Pvt. Ltd., Bangalore.
5.	Rotary compression machine (Rimek Mini Press-1)	Karnavathi Engineering Ltd, Gujarat.
6.	Friabilator (EF-2)	Friabilator, Electrolab, Mumbai.
7.	Monsanto hardness tester	Servewell Instruments and Equipment Pvt. Ltd., Bangalore.
8.	Dissolution apparatus (TDT-8)	Electrolab dissolution tester, Mumbai.
9.	Digital pH meter (7007)	Digisun Electronics, Hydrabad.
10.	Desiccators	Tarson, Culcutta.
11.	Vernier calipers	RK industries, India.
12.	Sieves	Filterwel test sieves
13.	Stability chambers	Lab-care, Mumbai.
14.	Fourier Transform Infrared spectroscopy	Shimadzu, Japan.

	(8400)	
15.	Differential Scanning calorimetry (200PC)	NETZSCH, Japan.

Method

Preparation of tablets by direct compression method:

The matrix tablets of mebeverine Hcl were prepared by employing various polysaccharides like Guar gum, Locust bean gum and Xanthan gum by direct compression method using 8mm flat-faced punch of 10 stations Rimek compression machine (M/s Karnawati Engg. Ltd. Ahmedabad). For the preparation of matrix tablets, the active ingredient was thoroughly mixed with polymer(s) using a mortar and pestle for 10 min. Magnesium stearate (1.5%w/w) and talc (3% w/w) were added to the above blend as flow promoters.

In all the formulations the amount of mebeverine Hcl was kept constant at 200 mg and the polymers Guar gum, Xanthan gum and Locust bean gum were used in different ratios (1:0.75 1:1, 1:1.25, and 1:1.5) with respect to drug. The formulae of different matrix tablets of mebeverine Hcl are given in the Table 2.

Preparation of tablets by wet granulation method:

In another set of formulations**,** wet granulation technique was adopted for the tablets containing psyllium husk alone and its combination with XG. All the components were screened and then thoroughly mixed in a bottle using tumbling method for a period of 15 mins. The powder mixture was granulated with 10% starch paste. The wet mass was passed through sieve # 16 and the granules were dried at 50°C for 2 h. in a hot air oven. The dried granules were passed through # 22. Lubricated with magnesium stearate and talc by further blending for 3 min. Compression was done on 10-station Rimek tablet compression machine (M/s Karnawati Engg. Ltd. Ahmedabad) using 8 mm flat faced punches.

TABLE 4: Composition of matrix tablets of mebeverine Hcl.S

Code	INGRIDIENTS (Mg/600mg of tablet)					
	Mebeverine Hcl	**GG**	**LBG**	**PH**	**XG**	**MCC**
G1	200	150	-	-	-	223
G2	200	200				173

G3	200	250	-	-	-	123
G4	200	300		-	-	73
L1	200	-	150	-	-	223
L2	200	-	200	-	-	173
L3	200	-	250	-	-	123
L4	200	-	300	-	-	73
P1*	200	-	-	150	-	163
P2*	200	-	-	200	-	113
P3*	200	-	-	250	-	63
P4*	200	-	-	300	-	13
X1	200	-	-	-	150	223
X2	200	-	-	-	200	173
X3	200	-	-	-	250	123
X4	200	-	-	-	300	73
GX4	**200**	**150**	**-**	**-**	**150**	**73**
LX4	**200**	**-**	**150**	**-**	**150**	**73**
PX4*	**200**	**-**	**-**	**150**	**150**	**13**

*Wet granulation, 10% starch paste as a granulating agent.

SAll tablets contain 1.5% w/w magnesium stearate and 3 % w/w talc.

Evaluation of Tablet

Swelling studies

The swelling of the polymers upon hydration by the test medium was determined by a method similar to the equilibrium weight gain method. Representative formulations from each set were analyzed for swelling behavior. The matrix tablets were weighed and placed in tared metallic baskets. These baskets were then immersed in 900 ml of phosphate buffer

of pH 6.8 and rotated at 100 rpm. At specified time intervals, the baskets containing the matrix tablets were removed, lightly blotted with tissue paper so as to remove excess water and weighed again. They were then placed back in the dissolution vessel as quickly as possible. The percent degree of swelling was calculated as follows:

Percent degree of swelling= [(Ws−Wd)/Wd] ×100

Where Ws is the weight of the swollen matrix at time t and Wd is the weight of the dry matrix. The swelling study was done in triplicate for all samples tested.

Dissolution studies

The prepared matrix tablets were subjected to *in-vitro* dissolution studies using an 8 station USP (TYPE I) dissolution apparatus (Electro Lab, TDT-O8L, Mumbai). The dissolution studies were carried out in pH 1.2 for 2 hrs & in pH 6.8 for next 22 hrs at 37± 0.5^0 C and 100 rpm. At regular time interval, 5 ml of sample was withdrawn from the dissolution medium and replaced with equal volume of fresh medium. After filtration and appropriate dilution, the samples were analyzed at 263nm for mebeverine Hcl against blank using UV-Visible spectrophotometer. The amount of drug present in the samples was calculated using standard curve.

Drug release studies in presence of rat caecal contents

For the optimized formulations, drug release studies were carried out using USP dissolution test apparatus (Type I, 100 rpm and 37± 0.5^0 C) by pH progression method and also in presence of rat caecal contents. The tablets were tested for drug release for two hrs in acid buffer of pH 1.2 as the average gastric emptying time is about two hrs. Then the dissolution medium was replaced with pH 6.8 phosphate buffer (900ml) and tested for drug release for 3 hrs as the average small intestinal transit time is about 3hrs (Satyanarayana S *et al*). After filtration and appropriate dilution, the samples were analyzed for mebeverine Hcl content at 263nm. Then the tablets were withdrawn and subjected for dissolution studies in presence of rat caecal contents.

To access the susceptibility of the prepared matrices to undergo degradation in the presence of the colonic bacteria, drug release studies were carried out in the presence of rat caecal content, since these are known to have similar content to that of human intestinal microflora. Swiss albino rats weighing 100-150g were selected for the presence study. These were maintained at a normal diet. To stimulate enzymes which specifically hydrolyze guar gum, Xanthan gum, locust bean gum, Psyllium husk, enzyme induction was done. For enzyme induction, 2ml of a 1 percent dispersion of guar gum, locust bean gum, Psyllium husk in water was administered to the rats daily for 7 days. For the removal of cecal content, 45 minutes prior to its

introduction in to the dissolution media, five rats were killed by decapitation. The abdomens of the rats were cut open, and the ceca were isolated, then tied on both the ends and cut. The cecal content was individually transferred to a previously weighed beaker containing 10ml of buffer pH 6.8 (previously bubbled with carbon dioxide). The weight of the pooled cecal content was taken. Carbon dioxide was continuously passed through the pooled content so as to keep the environment anaerobic (Sinha VR *et al*).

The drug release studies were carried out using USP dissolution test apparatus (Apparatus I, 100rpm and 37± 0.5^0 C) with slight modifications. The experiments were carried out using 100 ml of pH 6.8 phosphate buffer in a 150 ml beaker immersed in the water maintained in the jar, which in turn is in the water bath of the apparatus. The swollen formulations after completing dissolution study in acid buffer of pH 1.2 for 2hrs and pH 6.8 phosphate buffers were placed in the basket of apparatus and immersed in the dissolution medium containing rat caecal matter (4%w/v). The experiment was carried out with continuous carbon dioxide supply into the beaker. At the different time intervals, 5 ml sample was withdrawn without a pre-filter and replaced with 5 ml of fresh phosphate buffer containing caecal contents bubbled with CO_2 and the experiment was continued up to 19 hrs. After filtration and appropriate dilution, the samples were analyzed for mebeverine Hcl content at 263nm.The amount of drug present in the samples was calculated using standard curve.

Fourier Transform Infrared Spectroscopy (FTIR) study

The compatibility between drug and polymer was detected by IR spectra obtained on (Shimadzu 8400, Japan). The pellets were prepared on KBr- press (spectra lab,). The spectra were recorded over the number range of 4000 to 500cm^{-1}.

Differential scanning Calorimetry (DSC) study

Thermograms were obtained by using a differential scanning calorimeter (NETZSCH, DSC 200PC, Japan) at a heating rate 10^o C/min over a temperature range of 35-250^o C. The sample was hermetically sealed in an aluminium crucible. Nitrogen gas was purged at the rate of 10 ml/min for maintaining inert atmospheres.

Stability studies

The stability studies for the selected formulations were carried out according to ICH guidelines at 40□2^{o}C/75□5%RH for one month by storing the samples in stability chamber (Lab-care, Mumbai).

Fig5: IR spectra of pure drug mebeverine Hcl.

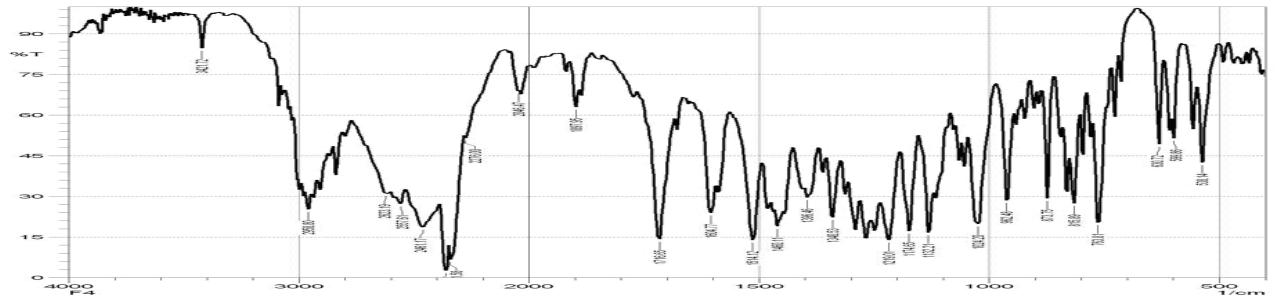


Fig6: IR spectra of GG matrix tablet of mebeverine Hcl (G4)

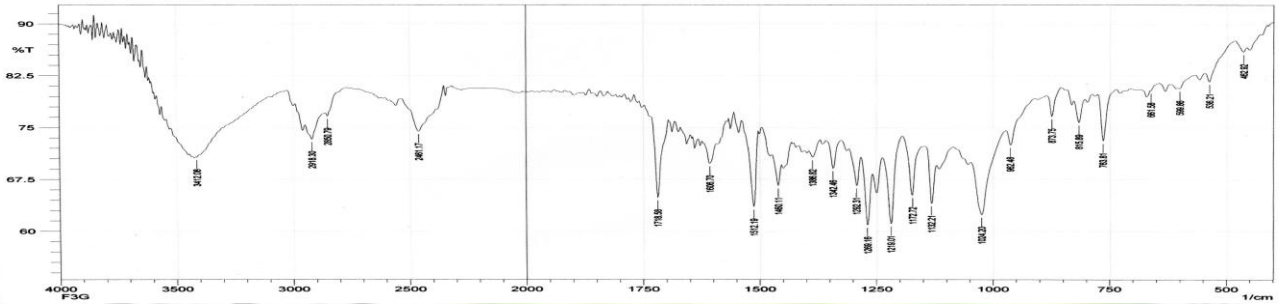


Fig7: IR spectra of LBG matrix tablet of mebeverine Hcl (L4)

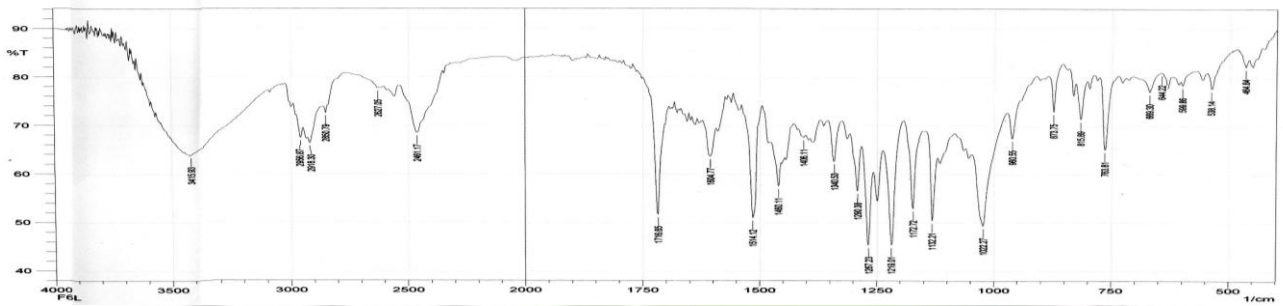


Fig 8: IR spectra of PH matrix tablet of mebeverine Hcl (P4)

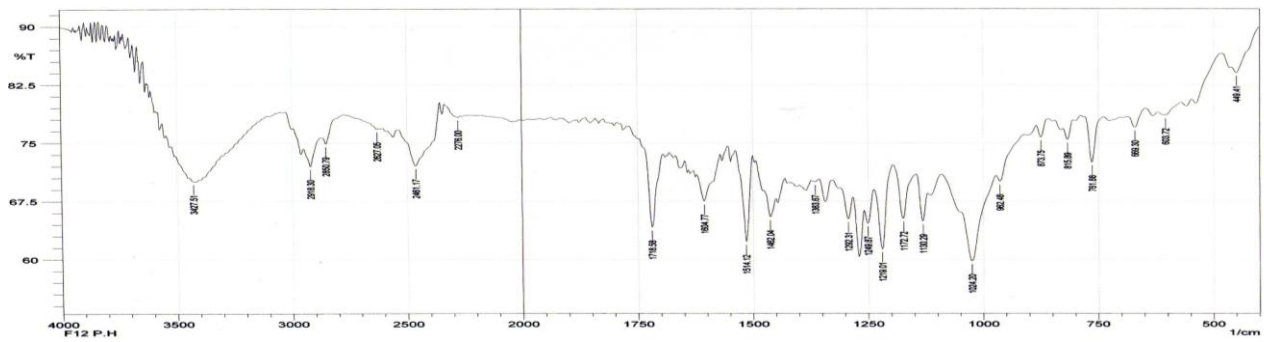


Fig 9: IR spectra of XG matrix tablet of mebeverine Hcl (X4)

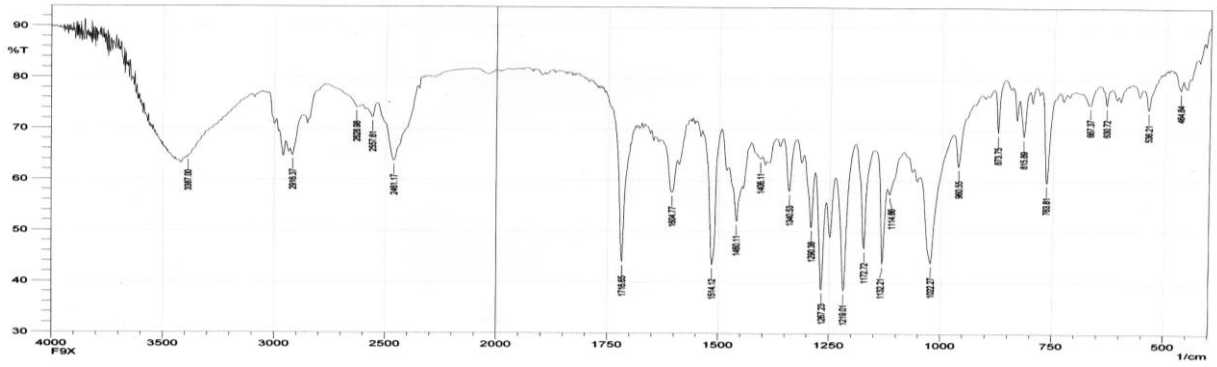


Fig10: IR spectra of PH-XG matrix tablet of mebeverine Hcl (PX4)

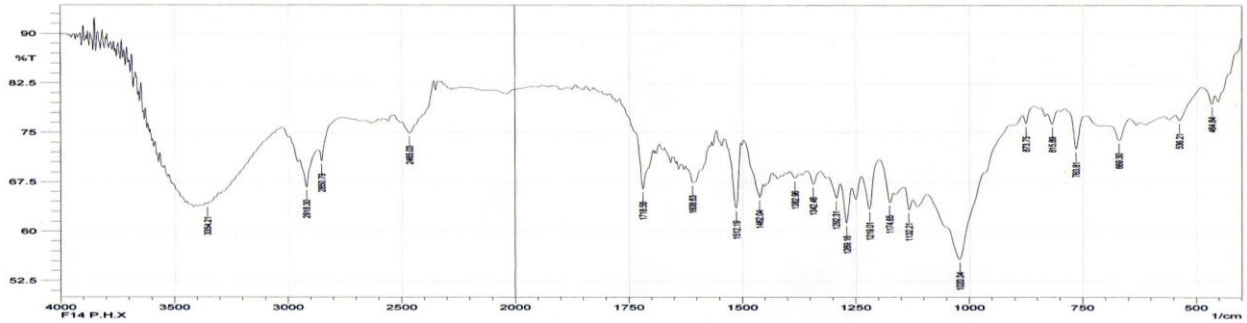


Fig11: DSC thermo gram of pure drug mebeverine Hcl

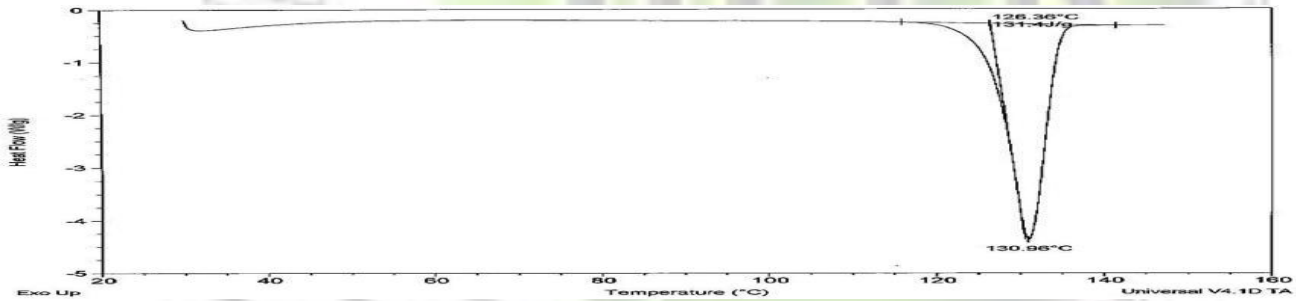


Fig12: DSC thermogram of GG matrix tablets of mebeverine Hcl (G4)

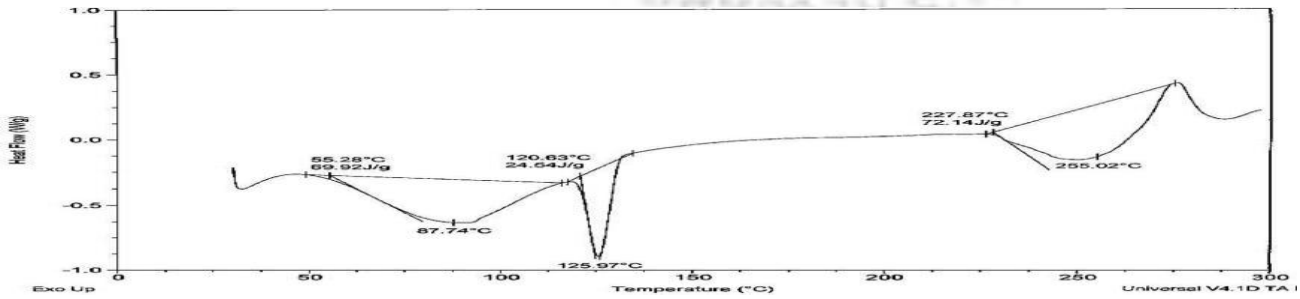


Fig13: DSC thermogram of LBG matrix tablet of mebeverine Hcl (L4).

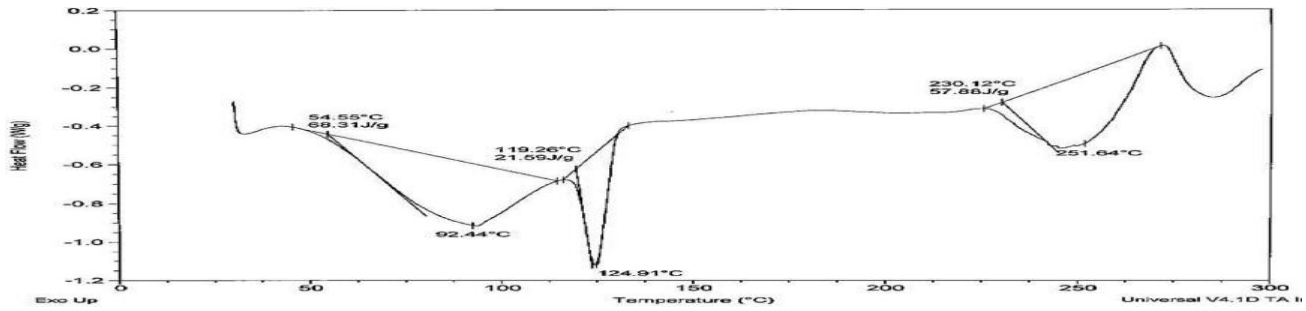


Fig14: DSC thermogram of PH matrix tablet of mebeverine Hcl (P4)

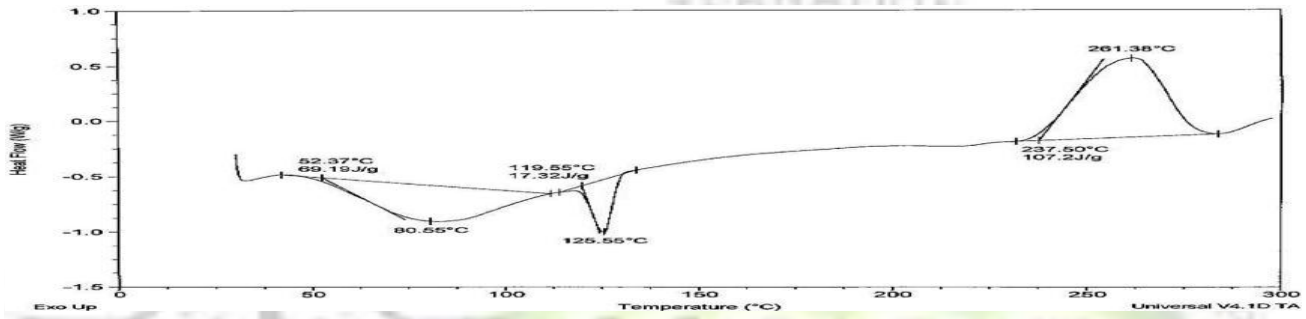


Fig15: DSC thermogram of XG matrix tablet of mebeverine Hcl (X4)

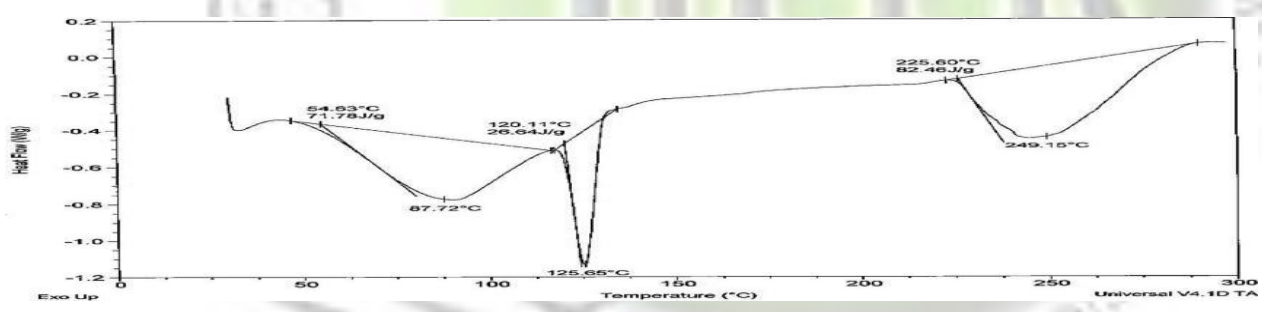


Fig16:DSC thermogram of PH-XG matrix tablet of mebeverine Hcl (PX4)

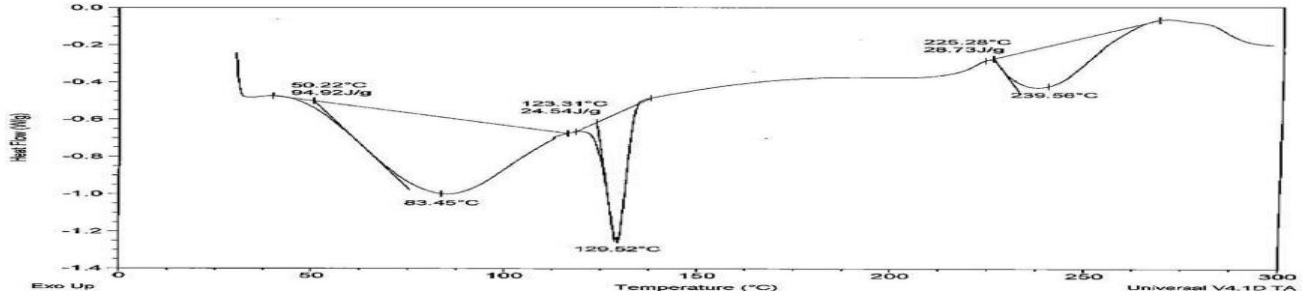


Fig17: Swelling study of GG matrix tablets of Mebeverine Hcl

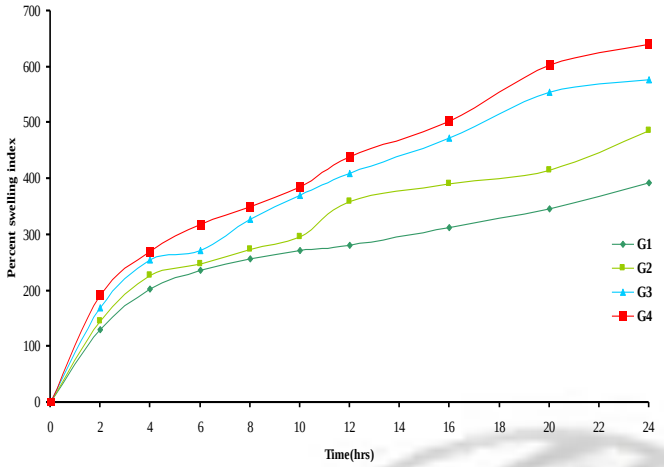


Fig18: Swelling study of LBG matrix tablets of Mebeverine Hcl

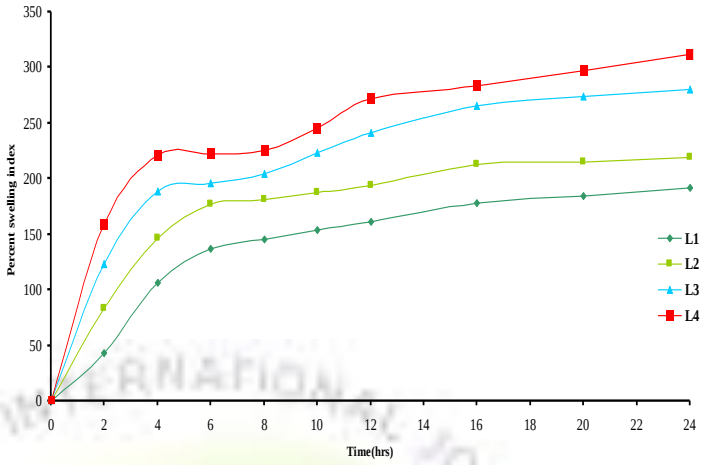


Fig19: Swelling study of PH matrix tablets of Mebeverine Hcl

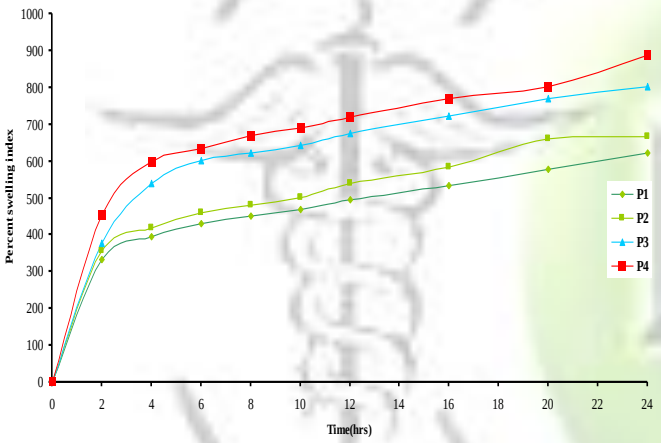


Fig20: Swelling study of XG matrix tablets of Mebeverine Hcl

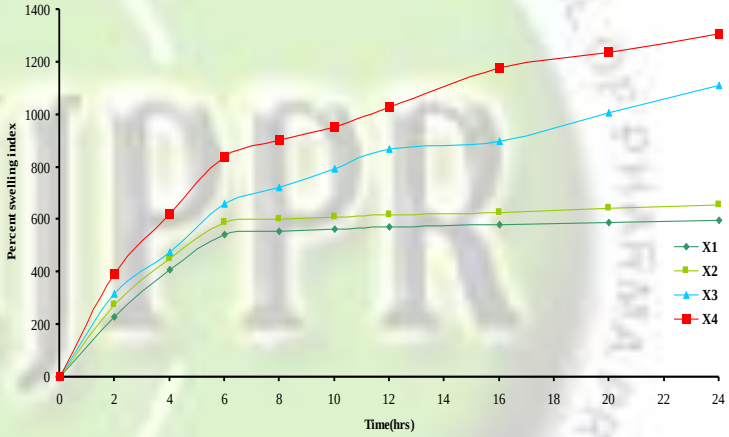


Fig21: Swelling study of PH matrix tablets of Mebeverine Hcl

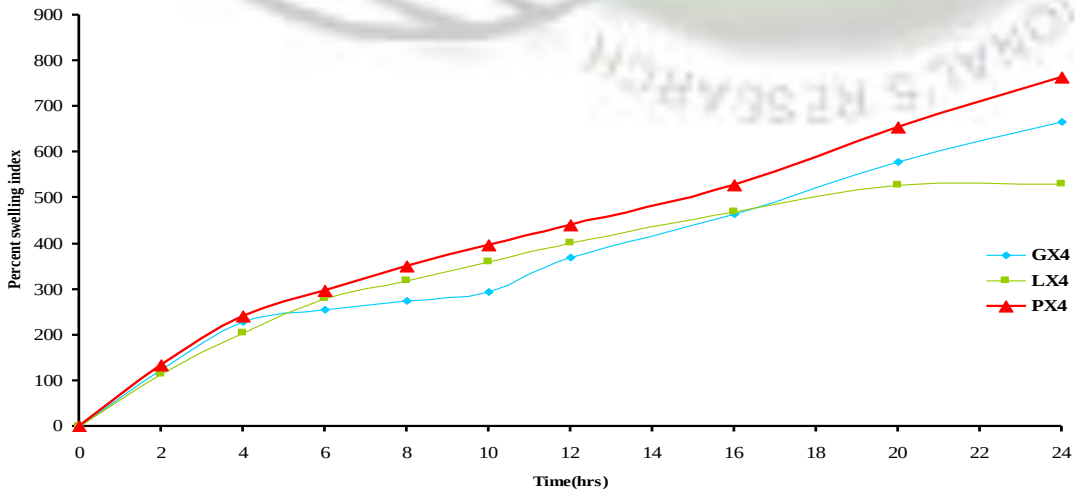


Fig22: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from GG matrix tablets

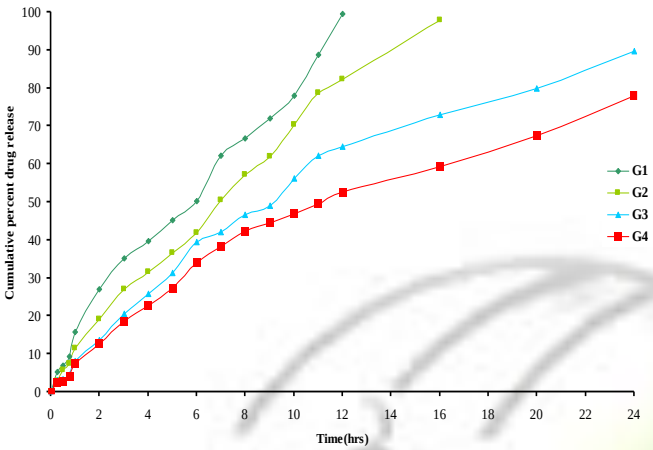


Fig 23: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from LBG matrix tablets

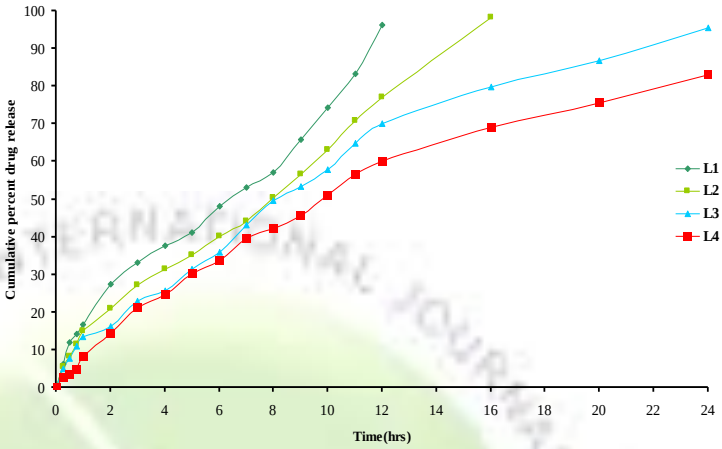


Fig24: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from PH matrix tablets

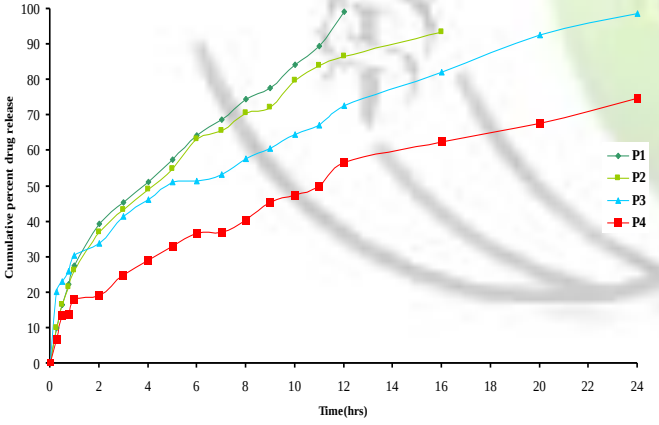


Fig25: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from XG matrix

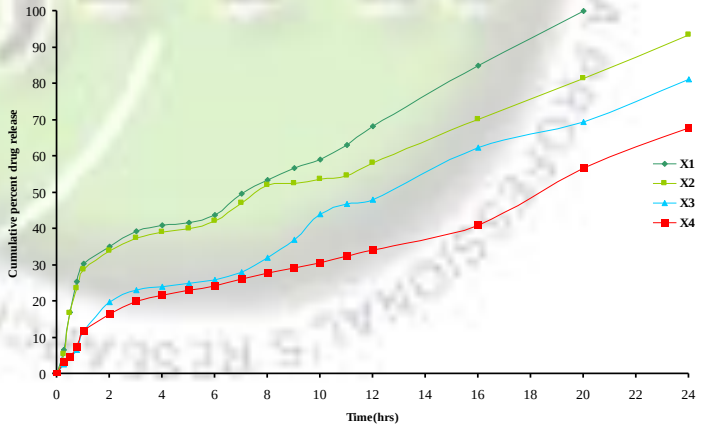


Fig26 : Effect of polymer combination on *in-vitro* release of Mebeverine Hcl from matrix tablets

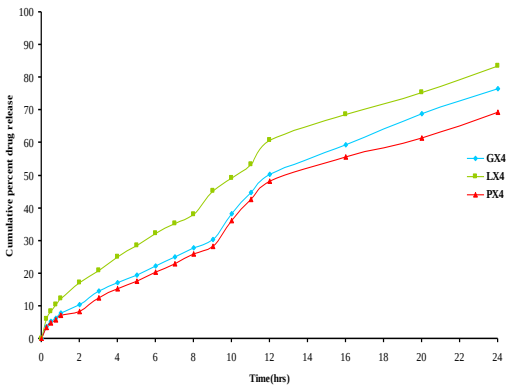


Fig27: Effect of *rat* caecal content on *in vitro* release of Mebeverine Hcl from GG, LBG, PH and XG-PH matrix tablets

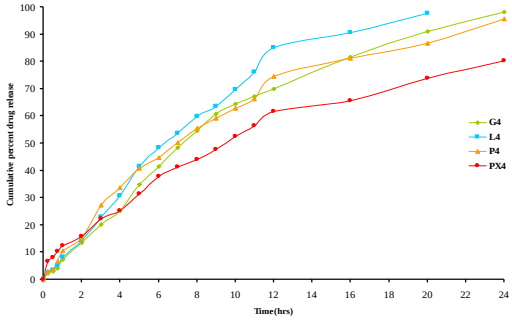


TABLE 5: Comparative drug release data of optimized GG (G4) and LBG (L4) matrix tablets in presence and absence of rat Caecal contents

Time (hrs)	G4		L4	
	Cumulative mean percent drug released		Cumulative mean percent drug released	
	Without caecal content	With 4% caecal content	Without caecal content	With 4% caecal content
4	22.76	25.30	24.64	30.77
8	42.30	54.50	42.11	59.95
12	52.62	69.90	60.13	85.07
16	59.24	81.55	69.20	90.69
20	67.45	91.13	75.51	97.79
24	78.02	98.14	83.01	---

TABLE 6: Comparative drug release data of optimized PH (P4) and XG-PH (PX4) in presence and absence of rat Caecal Contents

Time (hrs)	P4		PX4	
	Cumulative mean percent drug released		Cumulative mean percent drug released	
	Without caecal content	With 4% caecal content	Without caecal content	With 4% caecal content
4	29.02	34.77	15.28	25.29
8	40.29	56.37	25.89	44.08
12	56.77	73.35	48.37	61.60
16	62.69	81.99	55.61	65.63
20	67.77	91.07	61.43	73.76
24	74.73	98.26	69.32	80.37

Fig28: Comparative *in-vitro* release of Mebeverine Hcl from optimized GG matrix tablets with and without rat caecal content (G4)

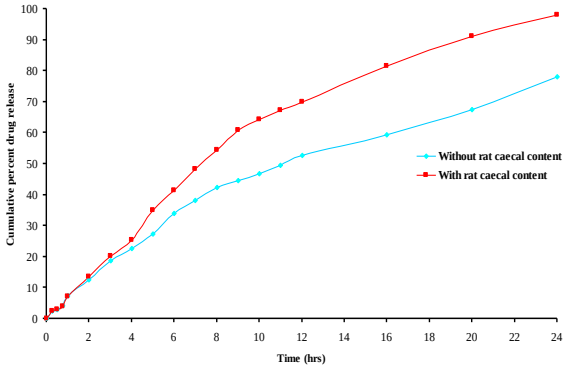


Fig29: Comparative *in-vitro* release of mebeverine Hcl from optimized LBG matrix tablets with and without rat caecal content (L4)

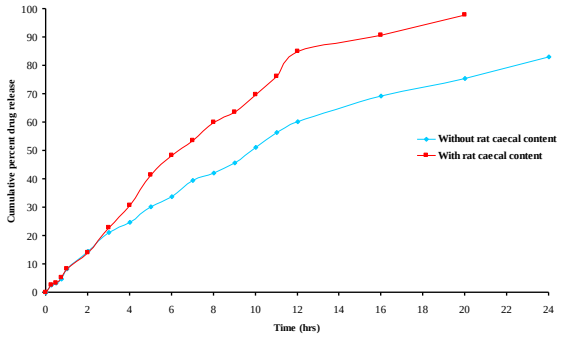


Fig30 : Comparative *in-vitro* release of mebeverine Hcl from optimized PH matrix tablets with and without rat Caecal content (P4)

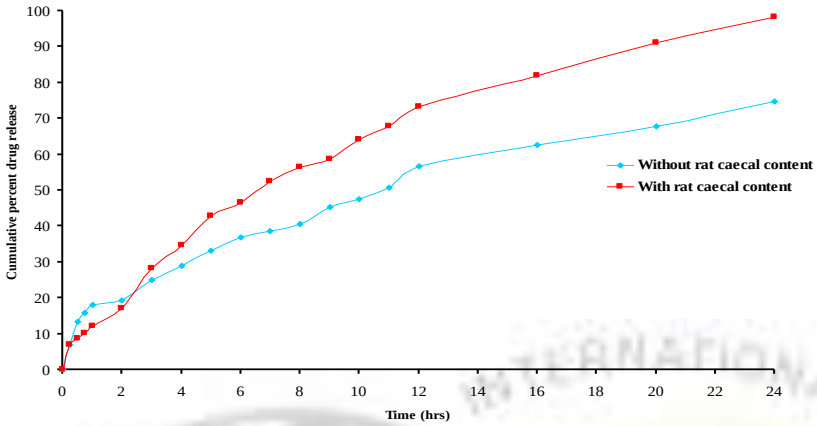


Fig31: Comparative *in-vitro* release of mebeverine Hcl from optimized PH-XG matrix tablets with and without rat caecal content (PX4)

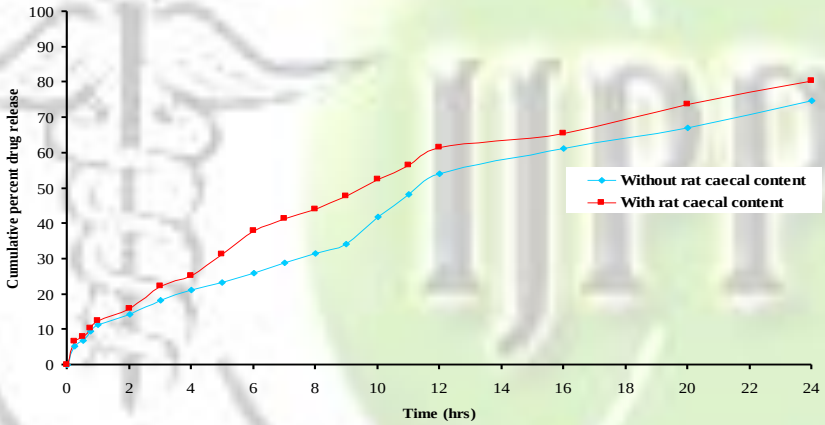
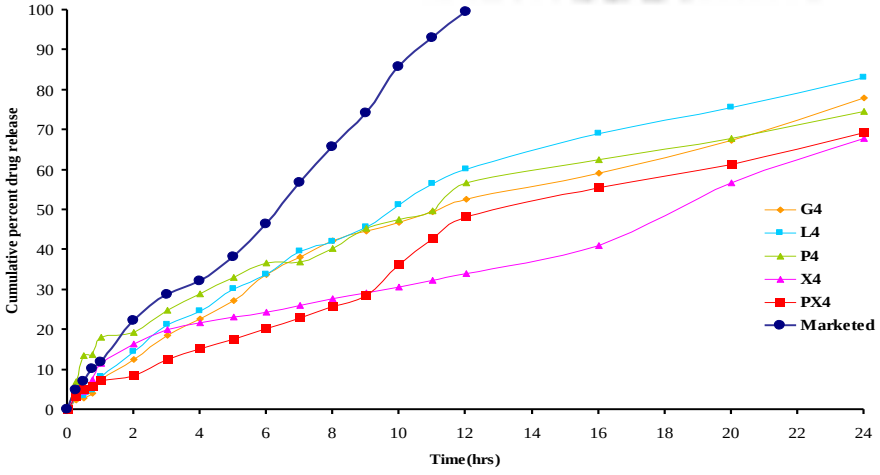


Fig32: Comparison of *in-vitro* release study of optimized formulations with marketed capsule (Colospa SR 200mg capsule) without caecal content



Kinetic analysis

Fig33: First order plot of selected matrix tablets of Mebeverine Hcl

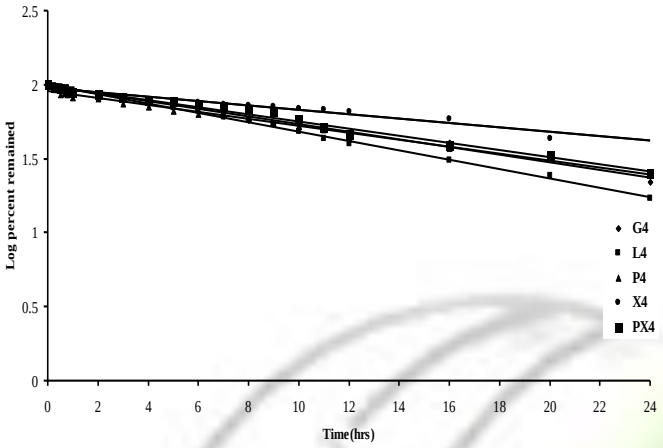


Fig34: Highuchi's plot of selected matrix tablets of Mebeverine Hcl

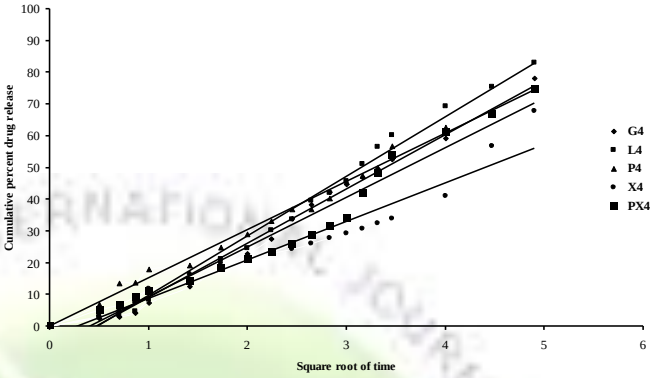


Fig 35: Korsmeyer-Peppas plot of selected matrix tablets of Mebeverine Hcl

Fig 36 : First order plot of selected matrix tablets of mebeverine Hcl in presence of rat caecal content medium

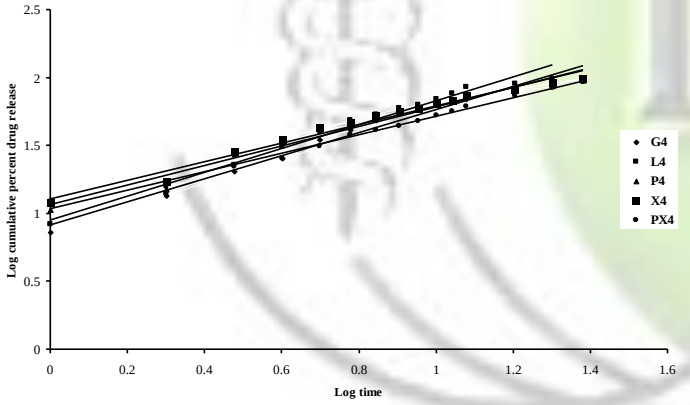


Fig37: Highuchi's plot of selected matrix tablets of mebeverine Hcl in presence of rat caecal content medium

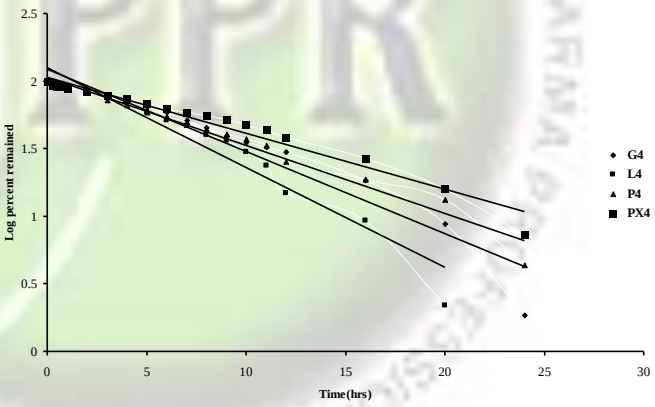
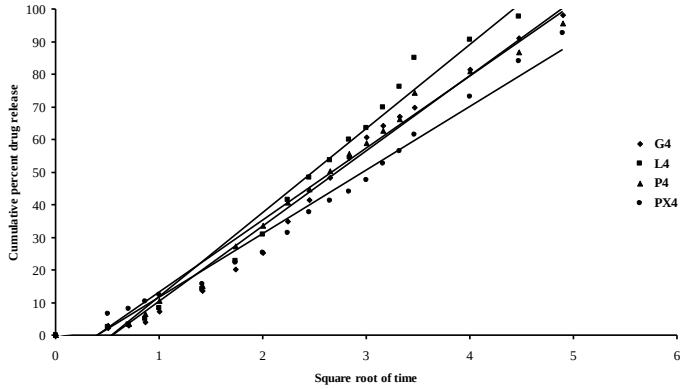


Fig38 :Korsmeyer-Peppas plot of selected matrix tablets of mebeverine Hcl in presence of rat caecal content medium



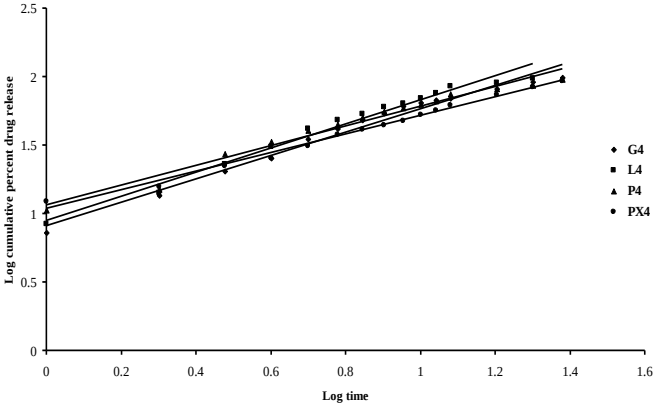


TABLE 7: Kinetic analysis (r2) of release data based on best curve-fitting method for different matrix tablets of Mebeverine Hcl (n=3)

Formulation code	Zero order		First order		Highuchi		Korsmeyer-peppas	
	N	r2	n	r2	n	r2	n	r2
G1	4.9341	0.9512	-0.0562	0.9843	22.247	0.9823	0.6602	0.9927
G2	5.4262	0.9496	-0.073	0.9615	24.889	0.9719	0.7607	0.99
G3	3.9714	0.9378	-0.0383	0.9887	20.308	0.9815	0.7769	0.9866
G4	3.3308	0.9376	-0.0259	0.9911	17.076	0.9864	0.7437	0.9864
L1	2.6721	0.9427	-0.0561	0.9821	22.786	0.9847	0.4923	0.9803
L2	5.068	0.974	-0.0697	0.8736	22.916	0.9688	0.6669	0.9826
L3	4.1535	0.9523	-0.0494	0.9572	21.013	0.9756	0.6935	0.9783
L4	3.6759	0.9436	-0.0316	0.9975	18.769	0.9847	0.737	0.9922
P1	4.4021	0.915	-0.0386	0.9929	14.287	0.9827	0.4802	0.9644
P2	4.909	0.8753	-0.0863	0.9186	23.671	0.9901	0.4619	0.9932
P3	3.5728	0.912	-0.0658	0.8335	18.582	0.9874	0.388	0.9732
P4	2.9411	0.928	-0.0234	0.9883	15.198	0.9919	0.4937	0.976
X1	4.1731	0.9517	-0.068	0.9985	16.286	0.9801	0.4032	0.9920
X2	3.2562	0.9038	-0.0374	0.9066	16.831	0.9665	0.3587	0.9227
X3	3.2705	0.9705	-0.0268	0.9689	16.25	0.959	0.5872	0.9443
X4	2.4535	0.9305	-0.0169	0.9646	21.83	0.9820	0.6049	0.9811
GX4	3.3944	0.9432	-0.028	0.9971	17.379	0.9896	0.6521	0.9938
LX4	3.5018	0.9624	-0.0306	0.99	17.624	0.9757	0.6482	0.9845
PX4	3.1429	0.9666	-0.0241	0.9838	15.633	0.9572	0.648	0.9644
Colospa Retard	3.8719	0.9718	-0.0389	0.9927	14.501	0.9760	0.412	0.9904

TABLE 8: Kinetic analysis (r2) of release data based on best curve-fitting method for selected matrix tablets of mebeverine Hcl in presence of rat caecal content medium (n=3)

Formulation code	Zero order		First order		Highuchi		Korsmeyer-peppas	
	N	r2	n	r2	n	r2	n	r2
G4	4.5001	0.9302	-0.0609	0.9832	23.048	0.9766	0.5528	0.9774
L4	5.5809	0.9381	-0.0736	0.9758	25.738	0.9706	0.4792	0.9789
P4	4.2268	0.9222	-0.0602	0.9878	21.889	0.99	0.4844	0.98
PX4	3.8777	0.9715	-0.0414	0.9996	19.468	0.9801	0.6797	0.9914

TABLE 9: Physico-chemical data of selected matrix tablets before and after stability study

Formulation code	Hardness test* (kg/cm^2)		Friability** (%)		Weight variation*** (%)		Thickness** (mm)		Drug content* (%)	
	before	After	Before	after	before	after	before	after	before	after
G4	6.5	6.5	0.94	0.98	1.39	1.41	5.79	5.78	98.81	98.82
L4	5.7	5.7	0.95	0.74	1.73	1.67	5.80	5.80	98.38	98.38
P4	6.9	6.8	0.90	0.87	1.07	1.13	5.86	5.85	99.35	98.21
X4	6.5	6.3	0.86	0.91	1.66	1.62	5.97	5.96	98.87	98.80
PX4	6.3	6.3	0.58	0.54	1.60	1.60	6.01	6.00	100.21	99.34

All values are expressed as mean ± SD, *n=5, **n=10, ***n=20

TABLE 10: Physico-chemical data of selected matrix tablets before and after stability study

Formulation code	$T_{50\%}$ (hrs)		$T_{75\%}$ (hrs)	
	before	after	Before	after
G4	11.40	11.56	23.07	23.21
L4	9.97	9.78	19.83	19.54
P4	10.56	10.61	---	---
PX4	14.38	14.12	---	---

*Average of three determinations

Physico-chemical evaluation of tablets:

Hardness (6kg/cm^2) and thickness (5-6 mm) were kept constant to avoid their effects on in *vitro drug* release. The tablets of different batches of GG, LBG, XG and PH alone and in combination were found to be uniform with respect to thickness (5.50 to 6.03 mm) and hardness (5.7 to 6.9 kg/cm^2). The friability (0.41 to 0.95 %) and weight variation (1.07 to 1.69 %) of different batch of tablets were found within prescribed limits. Drug content (96.01 to 100.21%) was found uniform within the batches of different tablets. Hence matrix tablets could be satisfactorily prepared by direct compression/wet granulation method. The results of physico-chemical evaluation of tablets are given in Table 5.

TABLE 11: FTIR study:

The pure drug mebeverine Hcl showed its characteristic absorption bands in the following IR regions.IR (KBr) cm^{-1}

Sl No.	Range	Group
1	3040 cm^{-1}	Aromatic C-H stretching
2	2958.80 cm^{-1} – 2800 cm^{-1}	(4 peaks) C-H stretching of CH_2 and OCH_3 groups. Both asymmetric and symmetric
3	2623 cm^{-1} – 2276 cm^{-1}	N-H stretching
4	1716.65 cm^{-1}	The sharp peak of C=O stretching of esters (veratrate).
5	1604 cm^{-1}, 1514 cm^{-1}, 1460 cm^{-1}	C=C ring stretching
6	1270 cm^{-1} – 1132 cm^{-1}	C-O-C asymmetric and C-O stretching
7	1024 cm^{-1}	C-O-C symmetric stretching
8	962 cm^{-1}	Substituted benzene ring
9	816 cm^{-1}	1-4 di-substituted benzene ring

The IR spectra of the formulation G4, L4, P4, X4 & PX4 showed their major peaks without significant shift in the positions of characteristic absorption bands in comparison with the IR spectrum of pure drug used in the present study. All these formulations showed their characteristic aliphatic C-H stretching in the same range (2960 cm^{-1} - 2800 cm^{-1}) as that of the pure drug. C=O stretch of all the formulations is at 1718 cm^{-1} which is in agreement with the C=O stretch of the pure drug. Similarly there is no appreciable change in the position of absorbance bands of C=C ring stretching. In all the formulations the C=C ring stretching is observed at 1604 cm^{-1}, 1514 cm^{-1}, 1460 cm^{-1}.

These facts clearly indicate that the pure drug has not undergone any change in its chemical identity even its different types of formulations with different polymers used in the present investigations. Thereby suggesting that there is no interaction between pure drug and polymers used for the different formulations. The results are shown in figure 5-10.

DSC Study:

The differential scanning calorimetry thermogram for pure drug mebeverine Hcl shows a sharp melting point at 130.96^{0}C, which is in agreement with the literature melting point of the drug. Similarly the DSC thermograms for the formulations F3, F6, F9, F12, and F14 showed the melting points as below:

Formulations	Melting point (^{0}C)
G4	125.97
L4	124.91
P4	125.65
X4	125.55
PX4	129.52

The thermograms of polymers do not show any marked difference in their melting points and also in the nature of the endothermic peak observed in comparison with the thermograms of the pure drug mebeverine Hcl. The negligible difference in the melting range may be due to variations in the type of the polymer used. Since there is no change in the thermal properties and nature of thermograms of the formulations and the pure drug, it may be concluded that the drug has not shown any interaction with different polymers used in preparing the different formulations. The results are shown in figure 11-16.

Thus from IR spectra studies and DSC thermograms we can draw a conclusion that the drug remains in its normal form without undergoing any interaction with the polymers.

Swelling study

Investigation of polymer swelling and erosion is a valuable exercise to better understand the mechanism of release and the relative importance of participating parameters. The swelling behavior indicates the rate at which the formulation absorbs water from the dissolution media and swells. In order to understand the dissolution behavior of the drug from the matrices, swelling studies were conducted under conditions similar to those used for the dissolution studies (Sinha VR *et al*). Visual observations showed that the matrices appeared swollen almost from the beginning and viscous gel mass was created when they came into contact with the dissolution medium. The change in weight of tablet is characteristic of the water uptake capacity and swelling was started immediately and continued for several hours depending upon the nature and concentration of the polymer. Matrix tablets of GG was found intact throughout the period of swelling in pH 6.8 phosphate buffer(24hrs) as compared to the tablets prepared with LBG, XG and PH. The swelling index of matrix tablets was directly proportional to the concentration of the polymer. On comparing the swelling index of various matrix formulations, it was observed that XG tablets (X1-X4) swelled more than that of GG (G1-G4), LBG (L1-L4), and PH (P1-P4). The swelling order of

polymers was XG>PH>GG>LBG. To know the synergistic effect of XG with other polymers on water uptake capacity of matrix tablets, three formulations (GX4, LX4 and PX4) were prepared by combining XG with GG, LBG and PH in 1:1 ratio and were subjected to swelling studies. Among all the polymeric blends studied, the combination of XG with PH (PX4) has greater swelling index than remaining combinations. Thus, matrix tablets containing XG alone and in combination with PH has shown better swelling capacity, however no reports are available on the synergistic gelling effect of XG with PH and hence further investigation in this direction is needed. Among all the polymeric matrices, the highest swelling was observed with those prepared using XG and the lowest with that of LBG. Our observations of swelling studies corroborates with those of Munday DL *et al* who studied the swelling behavior of XG, LBG and karaya gum matrix tablets. Overall, formulation (X4) showed greater swelling index (1308 %) than that of formulations G4 (640 %), L4 (312 %), P4 (886 %) and PX4 (764 %) at the end of 24 hrs. The order of swelling of optimized formulations was F16>F12 >F19>F4>F8. The results of swelling behavior of different matrix tablets were given in Table 5&6 and depicted in Fig 17-21.

In-vitro release study

The aqueous medium on contact with hydrophilic polymer matrix gradually begins to hydrate from the periphery towards the centre, forming a gelatinous swollen mass, which control the diffusion of drug molecules through the polymeric material in to aqueous medium. The hydrated gel layer thickness determines the diffusional path length of the drug. (Venkataraju *et al*). The ability of prepared tablets to retard drug release in the physiological environment of the stomach and small intestine, dissolution studies of the prepared matrix tablets were carried out in pH 1.2 for first 2hrs followed by pH 6.8 for remaining hours. The samples were analyzed for mebeverine Hcl content spectrophotometrically at 263nm.

Effect of polymer level:

To assess the influence of polymer level on drug release, 16 batches of matrix tablets were prepared using GG, LBG, XG and PH in different drug: polymer ratios like 1:0.75, 1:1, 1:1.25 and 1:1.5 (i.e. 25, 33.33, 41.66 and 50%w/w of the total tablet weight). The release data are depicted in Fig 22. The release studies conducted in pH 1.2 acid buffers revealed that only 12-27 % of drug was released from the prepared GG matrix tablets. This shows that guar gum is capable of protecting the drug from being released completely in the physiological environment of stomach. On exposure to the dissolution fluid of pH 6.8 phosphate buffer, GG matrix tablets of G1, G2, G3 and G4 have released about 99.43, 97.94, 89.67 and 78.02 % of mebeverine HCL at the end of 12^{th}, 20^{th} and

24th hr respectively. Increasing the polymer level from 1:0.75 to 1:1.5 has drastically retarded the drug release from the prepared matrix tablets. High release profiles were observed with polymer blend of 1:0.75 & 1:1 as compaired to 1:1.25 & 1:1.5 irrespective of nature of polymers. As the polymer level was increased, the gel layer formed is more likely to be resistant to the drug diffusion. It was also observed from the swelling study that the percentage of swelling index was proportionate with the polymer level. Hence the order of release profile from matrix tablet was comparable with its swelling index. The observation was in accordance with previous reports (Ganeshan V *et al)*.

The release patterns of LBG matrix tablets (L1-L4) made with drug-polymer ratio of 1:0.75, 1:1, 1:1.5 and 1:2 are shown in Fig 23 and Table 9-10. It showed that, the drug release was spread over an extended period of 12 to 24 hrs. The studies conducted in acid buffer of pH 1.2 showed 14-30 % of drug release, thus indicating the effectiveness of LBG in limiting the drug release in the physiological environment of the stomach. When the LBG matrix tablets were exposed to pH 6.8 phosphate buffers, complete release of drug was observed during the 24 hrs dissolution study. The order of release rate of drug from LBG matrices is L1 (96.17% at 12hrs) > L2 (98.20%, at 20th hr) > L3 (95.63% at 24hrs) > L4 (83.01% at 24hrs). As the proportion of LBG was increased there was a slight decrease in the release rate, but the polymer level has not affected drug release to a greater extent. The swelling of LBG was considerably less when compaired to other polymers, the similar effect was observed on *in vitro* release of the drug from the prepared matrix tablets. However the drug release could be controlled up to 24 hrs with the increase in polymer level (1:1.5). The observation was in accordance with the previous reports of Munday DL *et al*.

The release profile of PH matrix tablets indicated that, the release was spread over an extended period of 12 to 24 hrs. About 19-37 % of the drug was released in pH 1.2 acid buffers at the end of 2 hrs. The release of drug was directly dependent on the polymer level and the proportionate degree of swelling. Thus, the formulations with higher PH content swelled more and thereby controlled the drug release up to 24 hrs. In contrast to GG and LBG matrix tablets, release of drug from PH matrix tablets was slightly higher in the acidic pH. This could be due to higher solubility of mebeverine Hcl in the acidic pH (Sweetman SC *et al*) and another reason could be due to poor swelling of PH in acidic pH, thereby reduced path length for the diffusion of the drug. However the exact reason behind the higher release of mebeverine Hcl in acid medium from PH matrix tablets has to be explored. Controlled release of the drug was observed with phosphate buffer of pH 6.8. Drug release from matrix tablets of P1, P2,

P3& P4 was found 99.18%, 99.28%, 98.60 & 74.73 % respectively at the end of 12, 20 & 24hrs respectively in pH 6.8 phosphate buffer. In case of PH, polymer level has significant effect in controlling the drug release. The release rate was inversely proportional to the polymer level. This could be due to increase in concentration of polymer in the matrices. There was an increase in the amount of water uptake and proportionally greater swelling leading to a thicker gel layer around tablet, that led to a slower drug release. The results are in agreement with the observations made in the swelling studies. The observation was in accordance with previous reports of Hamman JH *et al*.

Through XG, a polysaccharide that is not degraded by the colonic bacteria, has been selected in the present study, as the combination of XG with other polymers showed synergistic effect in swelling and controlling the drug release (Sinha VR et al and Venkataraju MP *et al*). The *in vitro* release profiles of XG matrices as given in Fig 25 indicated the strong sustained release ability of the gum that extended over a period of 24 hrs. The release of drug from XG matrix tablets was also slightly higher (16-33% at the end of 2 hrs) in pH 1.2. The release was controlled after exposure of matrix to phosphate buffer of pH 6.8. Our observations of drug release in acidic pH were in accordance with Venkatraju *et al* who reported the initial burst of Xanthan gum erosion from the matrices during the acidic phase and there after erosion of xanthan gum slowed down considerably on exposure to higher pH. The release rates from tablets X1 was found to be 99.91 at the end of 20hrs, where as that of X2, X3 & X4 were 93.30, 81.12 and 67.79 % respectively at the end of 24hrs. As observed in case of other polymers, the drug release rate decreased in the order of increasing proportion of xanthan gum. It was reasoned that as the amount of XG in the matrix increased there would be a greater degree of gum hydration with simultaneous swelling. This would result in corresponding lengthening of the drug diffusion pathway and reduction in drug release rate (Munday DL *et al*). Swelling indices of XG also supported the results of *in vitro* drug release studies.

In conclusion, the drug release retarding ability of various gums investigated was in the order XG>PH>GG>LBG. Thus Xanthan gum has the ability to hydrate more rapidly than the other three gums used. The resulting drug diffusional path length for Xanthan gum was therefore the longest. Provided the gums have nearly similar diffusion coefficients, it would follow that the drug release rate from the Xanthan gum matrices would be the slowest (Munday DL *et al*). The *in vitro* drug release studies revealed that, level of the polymer in the matrix tablets played an important role in the modulation of drug release.

Effect of polymer blend:

To investigate the synergistic effect of XG with GG, LBG and PH, three batches of matrix tablets were prepared with polymer: polymer ratio of 1:1 and subjected to dissolution studies. About 8 to 17 % of the drug was released in pH 1.2 acid buffers at the end of 2 hrs. Interestingly, the release of drug from all the polymeric blend matrix tablets studied in acidic pH of 1.2 was lower than those observed for the tablets prepared with a single polymer. This could be due to synergistic interaction between the biopolymers to produce a strong and elastic gel around the core of the matrices (venkataraju *et al*). The release rates from GX4 (XG+GG), LX4 (XG+LBG) and PX4 (XG+PH) were found to be 76.68%, 86.23% and 74.84% respectively at the end of 24hrs in phosphate buffer of pH 6.8. The order of release from the matrix tablets prepared by combinations of polymers was PX4>GX4>LX4. The results can be compaired with swelling studies of same formulations wherein order of swelling was PX4>GX4>LX4. From the release studies, it can be observed that all the combinations can control the drug release over a period of 24hrs. Dissolution studies revealed that, XG has produced more synergistic effect with PH in controlling the drug release when compared to other combinations. The results were further supported by the swelling studies which showed the higher swelling index of XG with PH (764.57 %) compared to other polymeric blends (665 and 529% for XG+GG and XG+LBG respectively). Thus, XG controlled the drug release from matrices with alone and in combination of other polymers especially with PH. The release profiles were inversely proportional to the swelling index irrespective nature and combination of polymers.

Effect of rat caecal content:

To access the susceptibility of the prepared matrices to undergo degradation in the presence of the colonic bacteria, drug release studies were carried out in the presence of rat caecal content, since these are known to have similar content to that of human intestinal microflora (Sinha VR *et al*). Hence i*n vitro* release studies were carried out in phosphate buffer of pH 6.8 containing rat caecal matter for all the optimized formulations (G4, L4, P4 and PX4) except those containing xanthan gum alone as it is not degraded by colonic flora. However release studies incorporating caecal matter were carried out on optimized polymeric blend tablets (PX4 i.e. XG+PH). Initially the quantity of rat caecal content was kept at a lower level of 2%w/v and the release studies were carried for the optimized formulations. However no significant differences were observed in the release data of the formulations studied in presence and absence of caecal content. Hence the concentration of rat caecal content in the dissolution medium was increased to 4%w/v. Various reports are available which indicated satisfactory degradation of the gums in presence of 4 % caecal content (Sinha VR *et*

al, Satyanarayana V *et al*). To stimulate enzymes which specifically hydrolyze guar gum, locust bean gum and Psyllium husk, enzyme induction was done as described in the methodology.

The complete drug release was achieved (98.14%) at the end of 24hrs from GG matrix tablets (G4) in presence of 4%w/v caecal content as compaired to that of its absence (78.02%). This indicated the susceptibility of guar gum towards the colonic microflora and also the successful pretreatment of rats for the specific enzyme induction. Earlier studies performed by Rama Prasad *et al* on *in vitro* evaluation of guar gum as a carrier for colon specific drug delivery also proved that rat caecal medium at 4%w/v level obtained after 7 days of enzyme induction with 1 ml of 2% w/v GG dispersion provided the best conditions for assessing the susceptibility of GG to colonic bacterial degradation. From the dissolution studies it can be concluded that, the level of guar gum used (1:2) was sufficient for complete and controlled drug release in the presence of 4 % rat caecal content. The comparative release profiles of the optimized GG matrix tablets (F4) in absence and presence of 4 % rat caecal content is shown Table 5 and depicted in Fig: 28.

In vitro drug release studies of optimized LBG matrix tablets showed that, 97.17 % of the drug was released at the end of 20 hrs in presence of 4 % rat caecal contents, where as in the absence, 83% of drug was released at the end of 24. Increased drug release could be due to greater susceptibility of the LBG towards the caecal content and also due to the higher aqueous solubility of mebeverine Hcl. This signifies the need to increase the level of LBG (>50 % of total tablet weight) in the matrix tablets so as to achieve complete and controlled drug release in the physiologic conditions of the colon up to 24 hrs. Earlier reports of Raghavan CV *et al* also indicated the susceptibility of LBG to colonic bacterial enzymatic actions with resultant drug release in the colon.[47]

In vitro release studies carried out in presence of 4 % w/v caecal matter for the optimized PH matrix tablets (P4) revealed that 98.79% of the drug was released at the end of 24th hr compared to 74.73 % in the absence of caecal matter. Almost 25% of higher drug release was observed in presence of caecal matter, thus indicating that PH could be used as a microbially triggering agent in the colonic delivery of mebeverine Hcl. The present study indicated that, drug: PH ratio of 1:1.5 is sufficient in controlling the release of a water soluble drug mebeverine Hcl in the presence of 4% rat caecal matter.

The complete drug release was observed (82.69%) from PH-XG matrix tablets (PX4) at the end of 24hrs in presence of 4%w/v rat caecal content as compaired to that of its absence (69.32%), PH matrix tablets (P4) gave higher release profile (98.79%) as compaired to that of combination with XG. This could be

due the presence of XG which is not susceptible for the enzymatic action of colonic microflora and also its inheritant release retarding efficacy and thus it can be concluded that, in combination also drug release is dependent on degradation of PH alone and not XG by the caecal content.

In conclusion, the *in vitro* drug release studies carried out in presence of rat caecal contents revealed that, except XG all other gums are susceptible to the action of enzymatic degradation of the colonic bacteria. However the concentration of LBG used in the optimized formulation (L4) was found to be insufficient in controlling the drug release for 24hrs in presence of 4 % w/v of rat caecal contents. Thus from the study, it was clear that the developed matrix tablets containing the polysaccharides alone and in combination could control the drug release in the media mimicking the natural colonic conditions.

Comparison with marketed product:

The release profiles of optimized matrix tablets of mebeverine Hcl were compared with that of available marketed product (Colospa Retard 200mg capsule). The optimized tablets prepared using GG (G4), LBG (L4), PH (P4), XG (X4) and blend of gums XG-PH (PX4) showed controlled release over periods of 24 hrs, whereas the marketed product controlled the drug release over a period of 12 hrs. Hence the developed matrix tablets can be viewed as a better approach in the colonic delivery of mebeverine Hcl.

Mechanism of drug release:

To investigate the study the mechanism of drug release from the matrix tablets, various kinetics models like zero order, first order, Higuchi's and Korsmeyer-Peppas equations were applied to the *in-vitro* release data. As observed from the Table 21, the values of correlation-coefficient (R^2) for all the formulations were high enough to evaluate the drug dissolution behavior. The mechanism of drug release from the optimized GG matrix tablets (G4) was found to be diffusion controlled first order kinetics as the r^2 value of Highuchi equation and first order equation was found to be 0.9864 and 0.9911 respectively. Further the data was plotted in the Korsmeyer-Peppas equation revealed the existence of anomalous release profile as the n value observed was 0.7437. Thus the release of mebeverine Hcl from optimized GG matrix tablets followed non-Fickian diffusion controlled first order release kinetics.

When the drug release data of optimized LBG matrix tablets (L4) was subjected for kinetic analysis, the release mechanism was found to follow diffusion controlled first order as the r^2 value of Highuchi equation and first order equation was found to be 0.9847 and 0.9975 respectively. The kinetic analysis of *in vitro* release data showed anomalous diffusion controlled release as the n value of

Korsmeyer-Peppas equation was found to be 0.737. Thus similar to GG, the matrix tablets prepared with LBG also showed Non- Fickian diffusion controlled first order release kinetics.

The mechanism of drug release from optimized PH matrix tablets (P4) followed diffusion controlled first order as the r^2 value of Highuchi equation and first order equation was found to be 0.9919 and 0.9883 respectively. The n value of Korsmeyer-Peppas equation was found to be 0.4937. The release followed Non-Fickian diffusion as the value of n is >0.45 and <0.89 (Munday DL *et al*). Thus the release of drug from LBG matrix tablets followed non- Fickian diffusion controlled first order kinetics.

For optimized XG matrix tablets (X4), *in vitro* release data from 3rd hr of dissolution study was subjected for kinetic analysis as negligible amount of drug was released during this period. The mechanism of drug release followed Highuchi equation as the r^2 value was found to be 0.9820 followed by Korsmeyer-Peppas (0.9811). However the r^2 values of zero order (0.9305) and first order (0.9646) were not high enough to characterize exactly whether the release mechanism followed zero order or first order.

Mechanistic analysis of the release data was also carried for the tablets prepared using the combination of polymers. The optimized polymeric blend tablets (PX4) showed that, the release mechanism followed diffusion controlled first order kinetics as the r^2 values of Highuchi and first order equation were found to be 0.9572 and 0.9838 respectively. Further, data was analyzed by Korsmeyer-Peppas equation. It revealed that, the drug release was Non-Fickian diffusion type, as the n value was found to 0.648. Thus the kinetic analysis of polymeric blend tablets showed that the drug release followed anomalous diffusion controlled first order kinetics.

The drug release studies carried out in presence of rat caecal contents was also subjected to kinetic analysis. All the optimized formulations (G4, L4, P4 and PX4) in presence of 4% rat caecal content showed Non- Fickian diffusion controlled first order kinetics. However, smaller differences in the r^2 and n values were observed in the kinetic analysis of the release data obtained in presence and absence of caecal content. This could be altered release profiles of the matrix tablets in presence of rat caecal contents.

In conclusion, the kinetic analysis of the release data of the tablets prepared using GG (G4), LBG (L4), PH (P4) and combination of XG&PH (PX4) showed that, the drug release followed non- Fickian diffusion controlled first order kinetics. However the tablets prepared using XG (X4) followed Korsmeyer-Peppas equation. The mechanism of drug release in presence and absence of rat caecal content found to be similar with smaller changes in the kinetic values.

Stability studies:

The stability studies were carried out for the selected formulations (G4, L4, P4, X4 and PX4) at 40±2^{o}C/ 75±%5 RH as per ICH guidelines for a period of one month. Table 9-10 shows the values of post-compressional parameters before and after stability studies. The results indicated that, the tablets did not show any physical changes (hardness and friability) during the study period. The drug content was found above 98% at the end of one month. The study indicated that, tablets remained fairly stable during storage conditions.

Conclusion:

- The following conclusions were drawn from the results obtained.
- Preformulation studies on mebeverine Hcl fairly corroborates with the reported literature limits.
- The adopted methods yielded uniform and reproducible matrix tablets with all the polysaccharides used.
- The hardness, friability, weight variation, drug content, swelling index and in vitro release were uniform and reproducible.
- The percentage swelling index was found to be directly proportional to the polymer concentration irrespective of nature of the polymer used.
- Swelling studies indicated that, matrix tablets prepared with XG swelled more than other polymers. The order of swelling was XG>PH>GG>LBG for tablets prepared with single polymer and (XG+PH)>(XG+GG)>(XG+LBG) with combinations.
- The results of swelling studies correlate with the release behavior of the drug.
- The drug release was inversely proportional to the polymer concentration irrespective of nature of the polymer used. XG gave better controlled release as compared to other polymers.
- Presence of rat caecal content has enhanced the release profiles of polysaccharide matrix tablets except XG, due to enzymatic degradation by colonic bacteria.
- Combination of XG with PH gave better controlled release than that of alone and other combinations.
- The mechanism of drug release was Non-Fickian diffusion controlled first order kinetics for optimized matrix tablets of GG (G4), LBG (L4) and XG+PH (PX4) where as for XG tablets (X4) followed Highuchi model.
- The controlled release profiles of optimized matrix tablets were found superior than the marketed product.
- FT-IR and DSC studies of optimized formulations G4, L4, P4, X4 and PX4

revealed no chemical interaction between drug and polymers used.

- Selected matrix tablets were found to be stable with respect to drug content, friability, weight variation and release profiles during the stability study period.
- Hence, microbially triggered polysaccharide colon specific matrix tablets of mebeverine Hcl showed promising results and there exist a scope for in vivo evaluation using suitable animal models.

References

1. http://digestive.niddk.nih.gov/ddiseases/pubs/ibs_ez/.
2. http://:www.wikipedia.org/wiki/mebeverine.
3. Sweetman SC. Martindale – The complete drug reference. Gastro – intestinal drugs. 34th Ed Press London 2005; 1273-1.
4. Dickinson RG, Baker PV, Franklin ME and Hooper WD. Facile hydrolysis of mebeverine in vitro and in vivo: negligible circulating concentration of the drug after oral administration. J Pharm Sci 1991; 80: 952-57.
5. Ciftci, k. Alternative approaches to the treatment of colon cancer. Eur J Pharm Biopharm 1996; 42, 160-70.
6. Hauner, S.B. Inflammatory bowel disease. N Engl J Med 1996; 334:841-48.
7. MacFarlane GT, Cummings JH, MacFarlane S, Gibson GR. Influence of retention time on degradation of pancreatic enzymes by colonic bacteria grown in 3 stages continuous culture system. J Appl Bacteriol 1989; 675:21-27.
8. Haupt S, Rubinstein A. The colon as a possible target for orally administered peptide and protein drugs. Crit Rev Therap Drug Carr Syst 2002; 19(6): 499-551.
9. Vassallo M, Camilleri M, Phillips SF, Brown ML, Chapman NJ, Thomforde GM. Transit through the proximal colon influences stool weight in the irritable bowel syndrome. Gastroenterology, 1992; 102:102-08.
10. Reddy SN, Bazzocchi G, Chan S, Akashi K, Villanueva-Meyer J, Yanni G, MenaI, Snape WJ. Colonic motility and transit in health and ulcerative colitis. Gastroenterology 1991; 101: 1289-97.
11. El-massik MA, Nasra MA, Naggar VF. Development of metronidazole colon-specific delivery system. Asian journal of pharmaceutical sciences 2007;2(1): 18-28.
12. Jain A, Gupta Y, Jain SK. Perspectives of Biodegradable Natural Polysaccharides for Site-Specific Drug Delivery to the Colon. J Pharm Pharmaceut Sci 2007; 10 (1): 86-128.
13. Krishna K, Tanaji N, Kiran B, Pradeep D. Studies on development of oral colon targeted drug delivery system of locust bean and Xanthan gums. International journal of green pharmacy 2007; (1): 33-36.
14. Al-saidan SM, Krishnaiah YSR, Patro SS, Satyanaryana V. *In vitro* and *in vivo* of guar gum matrix tablets for oral controlled release of water-soluble Diltiazem HCL. AAPS Pharm Sci Tech 2005; 6(1).
15. Hamman JH, Beneke CE, Viljoen AM. Polymeric plant derived excipients in drug delivery. http://www.mdpi.com/journals/molecules Molecules 2009; 14: 2602-20.
16. Sinha VR, Kumria R. Polysaccharide matrices for microbially triggered drug delivery to the colon. Drug Dev Ind Pharm 2004; 30(2): 143-50.
17. http://dissertations.ub.rug.nl/FILES/faculties/science/2005/r.steendam/c2.pdf (15th Jan, 2009).
18. Brazel CS, Peppas NA. Dimensionless analysis of swelling of hydrophilic glassy polymers with subsequent drug release from relaxing structures. Biomaterials 1999 Apr; 20 (8): 721-32.
19. Brazel CS, Peppas NA. Modeling of drug release from swellable polymers. Eur J Pharm Biopharm 2000 Jan; 49 (1): 47-58.
20. Siepmann J, Peppas NA. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). Adv Drug Dev Rev 2001; 48:139-57.
21. Peppas A et al, A simple equation for description of solute release I. Fickian and non-Fickian release from non-swellable devices in the form of slabs, spheres, cylinders or discs. J Con Rel 1987: 5; 23-36.
22. http://dissertations.ub.rug.nl/Files/faculties/science/2005/r.steendam/c2.pdf (15th Jan, 2010)
23. Reza MS, Quadir MA, Haider SS. Comparative evaluation of plastic, hydrophobic and hydrophilic polymers as matrices for controlled-release drug delivery. J. Pharm Sci 2003; 6(2): 282-91.
24. Omar S, Aldosary B, Refai H, and Gohary OA. Colon specific drug delivery for mebeverine HCL. Journal of Drug Targeting 2007; 15(10): 691-700.
25. Dandagi PM, Mastiholimath VS, Gadad AP, Kulkarni AR, Konnur BK. PH-sensitive

mebeverine microspheres for colon delivery. Indian J pharm Sci 2009; 71(4): 464-68.

26. Gohary O, Abd Ei Hady SS, Dabis NA. Sustained release matrix of mebeverine HCL using polyacrylate resin "Eudragit retard" kinetics of drug release and evaluation of a kinetic model. Drug Dev Ind Pharm 1991; 17(15): 2055-65.
27. Al-dossary BN, Al-Gohary OMN, El-khawaas MM. *In-vitro* and *in-vivo* availability of mebeverine HCL suppositories. Sci Pharm 2006; 74: 31-51.
28. Satyanarayana S, Krishnaiah YSR, Rama Prasad YV. *In vitro* evaluation of guar gum as a carrier for colon-specific drug delivery. J Control Rel 1998; 51:281-87.
29. Ahrabi SF, Madsen G, Dyrstad K, Sande SA, Graffner C. Development of pectin matrix tablets for colonic delivery of model drug ropivacaine. Eur J pharm Sci 2000; (10): 43-52.
30. Shidhaye S, Kadam VJ, Desai A. Possible use of Psyllium husk as a release retardant. Indian J pharm Sci 2007; 69(2): 206-10.
31. Pandit KJ, Senapati MK, Srinatha A. *In vitro* release characteristics of matrix tablets: Study of karaya gum and guar gum release modulators. Indian J Pharm Sci 2006; 68(6): 824-26.
32. Venkataraju MP, Gowda DV, Rajesh KS, Shivakumar HG. Xanthan and locust bean gum (from *Ceratonia siliqua)* matrix tablets for oral controlled delivery of propranolol HCL. Asian journal of pharmaceutical sciences 2007; 2(6): 239-48.
33. Munday DL, Cox PJ. Compressed Xanthan and karaya gum matrices: hydration, erosion and drug release mechanisms. Int J Pharm 203; (2000): 179-92.
34. Deshmukh VN, Singh SP, Sakarkar DM. Formulation and evaluation of sustained release metoprolol succinate tablet using hydrophilic gums as release modifier. Int J PharmTech Res.2009; 1(2); 159-63.
35. Radwan MA, Foda NH, Al-deeb OA. Analytical profiles of drug substances and excipients. Volume 25: 165-207.
36. Rowe RC, Sheskey PJ, Weller PJ. Handbook of pharmaceutical excipients. Fourth ed. London: The Pharmaceutical Press; 2003.
37. Kokate CK, Purohit AP, Gokhle SB. Pharmacognosy. 13th Ed, Nirali prakashan: 2005.
38. www.The Superfoodco.co.uk.The premium superfood suppliers/dose of Psyllium husk2.mht.
39. Ministry of health and family welfare. Indian pharmacopoeia. Delhi: Controller of publications; 1996.
40. Mutalik S, Naha A, Usha AN, Ranjith AK, Musmade P, Manoj K, Anju P and Prasanna S. Preparation, *in vitro*, preclinical and clinical evaluation of once daily sustained release tablet of aceclofenac. Arch Pharm Res 2007; 30 (2): 222-34.
41. Lieberman HA, Lachman L and Schwartz JB. Pharmaceutical dosage forms: Tablets, Vol 2; Marcel Dekker, New York; 1990: 201-43.
42. Lakade SH, Bhalekar MR. Formulation and evaluation of sustained release matrix tablet of anti-anginal drug, influence of combination of hydrophobic and hydrophilic matrix former. Research J Pharm and Tech 2008; 1(4): 410-13.
43. Gupta AK. Introduction to pharmaceutics. Vol 1; 1993: 270. .

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