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Influence of Selected Natural Polymers on *In-vitro* Release of Colon Targeted Mebeverine HCl Matrix Tablet

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Abstract

The objective of the present study was to develop and evaluate colon specific matrices of mebeverine HCl using various polysaccharides like guar gum, Locust bean gum and xanthan gum by direct compression method. The matrix tablets were evaluated for their physico-chemical properties, swelling study, *in-vitro* release study and stability studies. 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 (X4) swelled more as compared to those prepared using GG and LBG. Release profiles indicated that, increase in the polymer concentration has drastically retarded the release of Mebeverine Hcl. The optimized tablets prepared using GG (G4), LG (L4) & XG (X4) showed controlled release over periods of 24 hrs, whereas the marketed product controlled the drug release over a period of 12 hrs. The mechanism of drug release was Non-Fickian diffusion controlled first order kinetics for optimized matrix tablets of GG (G4) and LBG (L4) where as for XG (X4) it followed Highuchi model. The developed matrix tablets can be viewed as a better approach in the colonic delivery of Mebeverine HCl.

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***Key words*:**
Irritable bowel syndrome; Mebeverine Hcl; Colon specific; Polysaccharides; *In- vitro* release;

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INTRODUCTION

Irritable bowel syndrome (IBS) is a disorder characterized most commonly by cramping, abdominal pain, bloating, constipation and diarrhea. 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 hydrochloride 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].

There has been an increasing interest in the development of site-specific systems for the release of drugs in the colon[4]. 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. Patients with irritable bowel syndrome [7] and ulcerative colitis [8] exhibited accelerated transit through different regions of the colon. 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 [9]. 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 [10].

Among the various systems developed for colon-specific drug delivery, prodrug and polysaccharides based delivery systems rely upon the enzymatic degradation of the carriers in the colon, there by resulting in the drug release. The inherent bacterial flora present in the colon carries out this enzymatic degradation. The enzyme-trigger mechanism in such delivery systems makes them highly site-specific. Prodrugs, however, can only be formed with a limited number of drug moieties due to a chemical linkage required in their formation. Further, as new chemical entities, pro-drug require a detailed toxicological study to be performed before being used as drug carriers. However, Natural polysaccharides, fall under the category of "GRAS" (Generally regarded as safe), thus resolving the general problems associated with safety[11]. 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[12]. 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[13].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[14]. 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[15].

Thus, the present investigation is aimed at using the inexpensive, naturally occurring and abundantly available polysaccharides for colon-targeted drug delivery.

EXPERIMENTAL METHODS

Materials:

Mebeverine Hcl was gifted by Rentus Pharma Pvt. Ltd., Andhrapradesh. Guar gum, Xanthan gum and locust bean gum were gifted by crystal colloid, Mumbai. Other excipients like, starch, microcrystalline cellulose, talc and magnesium stearate were purchased from S.D. Fine Chemicals Pvt. Ltd., Mumbai. All other reagents were analytical grade.

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. 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 were used in different ratios (Drug : Polymer = 1:0.75 1:1, 1:1.25, and 1:1.5 (w/w) named G1-4 for gaur gum, L1-4 for locust bean gum and X1-4 for xanthan gum polymer) with respect to drug. The formulae of different matrix tablets of Mebeverine Hcl are given in the Table 1.

Evaluation of matrix tablets:

Physico-chemical characterization: The prepared matrix tablets were evaluated for Hardness, Friability, weight variation, Uniformity of thickness, stability study, FT-IR and DSC characterizations using reported methods.

Uniformity of drug content: For determination of drug content at least three tablets from each formulation were weighed individually, crushed and diluted to 100ml with sufficient amount of phosphate buffer of pH 6.8. Then aliquot of the filtrate was diluted suitably and analyzed spectrophotometrically at 263 nm against blank[16].

Table 1: Composition of matrix tablets of Mebeverine Hcl[s]

Ingredients	G1	G2	G3	G4	L1	L2	L3	L4	X1	X2	X3	X4
Mebeverine Hcl	200	200	200	200	200	200	200	200	200	200	200	200
Guar gum	150	200	250	300	-	-	-	-	-	-	-	-
Locust bean gum	-	-	-	-	150	200	250	300	-	-	-	-
Xanthane gum	-	-	-	-	-	-	-	-	150	200	250	300
Microcrystalline- Cellulose	223	173	123	73	223	173	123	73	223	173	123	73

[s]All tablets contain 1.5% w/w magnesium stearate and 3 % w/w talc.

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[17]:

$$\text{Percent degree of swelling} = \frac{W_s - W_d}{W_d} * 100 \quad \text{---------- 1}$$

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, Electro Lab, TDT-O8L, Mumbai) dissolution apparatus. 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° 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.

Result and discussion

Physico-chemical evaluation of tablets: Hardness (6kg/cm²) 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 and XG were found to be uniform with respect to thickness (5.50 to 6.03 mm) and hardness (5.7 to 6.9 kg/cm²). 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 99.89%) was found uniform within the batches of different tablets. Hence matrix tablets could be satisfactorily prepared by direct compression. The FT-IR characterizations 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 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.

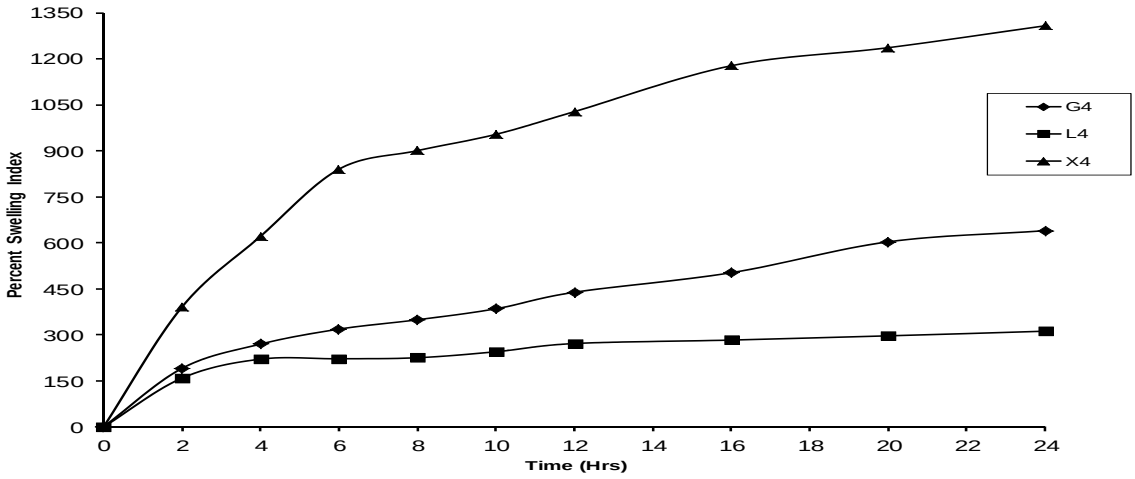

Fig 1: Comparison of swelling study of Optimized formulations

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.

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 and XG. 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) and LBG (L1-L4). The swelling order of polymers was XG>GG>LBG. Among all the polymeric matrices, the highest swelling was observed with those prepared using XG and the lowest with that of LBG [18]. Overall, formulation (X4) showed greater swelling index (1308 %) than that of formulations G4 (640 %) and L4 (312 %) at the end of 24 hrs. The results of swelling behavior of different matrix tablets were depicted in Fig 1.

***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[19]. 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. 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.

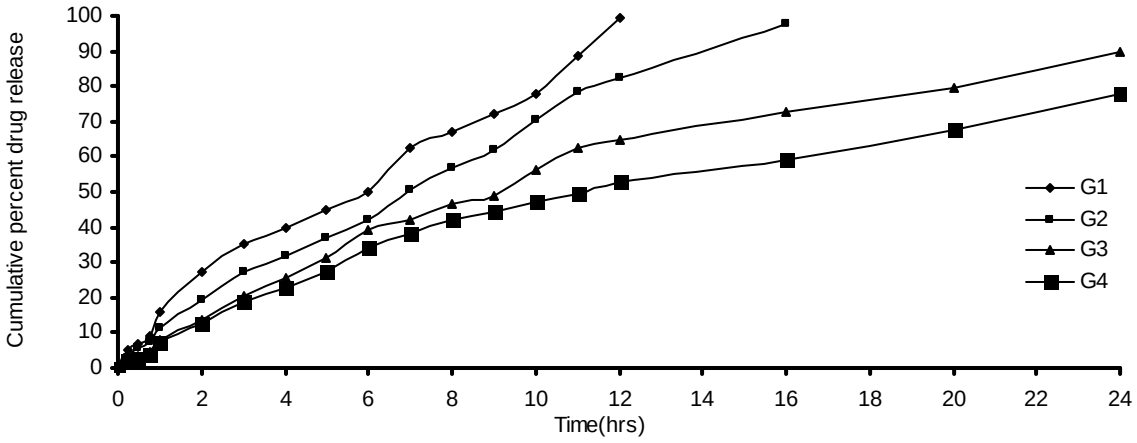

Fig 2: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from GG matrix tablets

Effect of polymer level: To assess the influence of polymer level on drug release, 12 batches of matrix tablets were prepared using GG, LBG and XG in different drug: polymer ratios like 1:0.75, 1:1, 1:1.25 and 1:1.5. The release pattern is depicted in Fig 2. 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 12th, 20th 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 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 [20-21] 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.

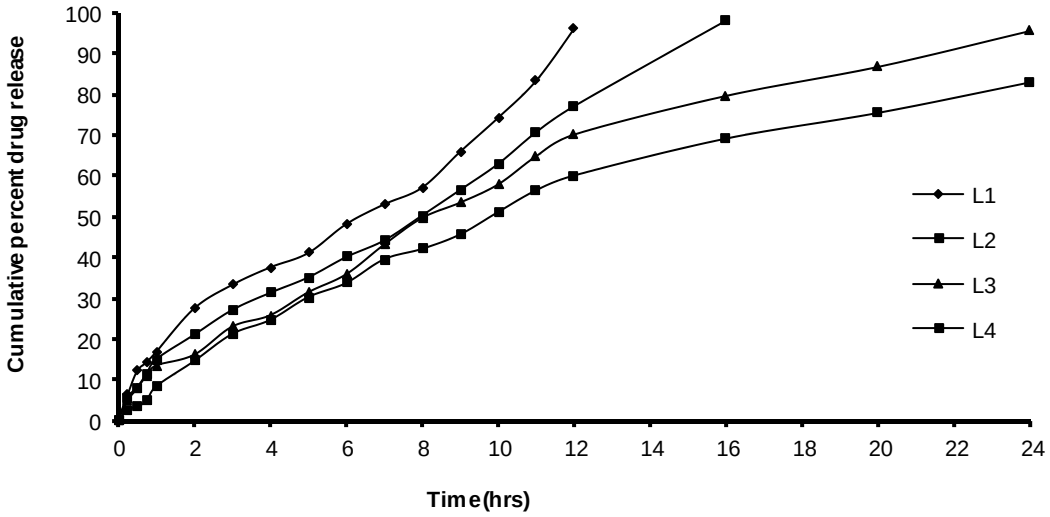

Fig 3: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from LBG matrix tablets

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 3. 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 compared 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*. 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.

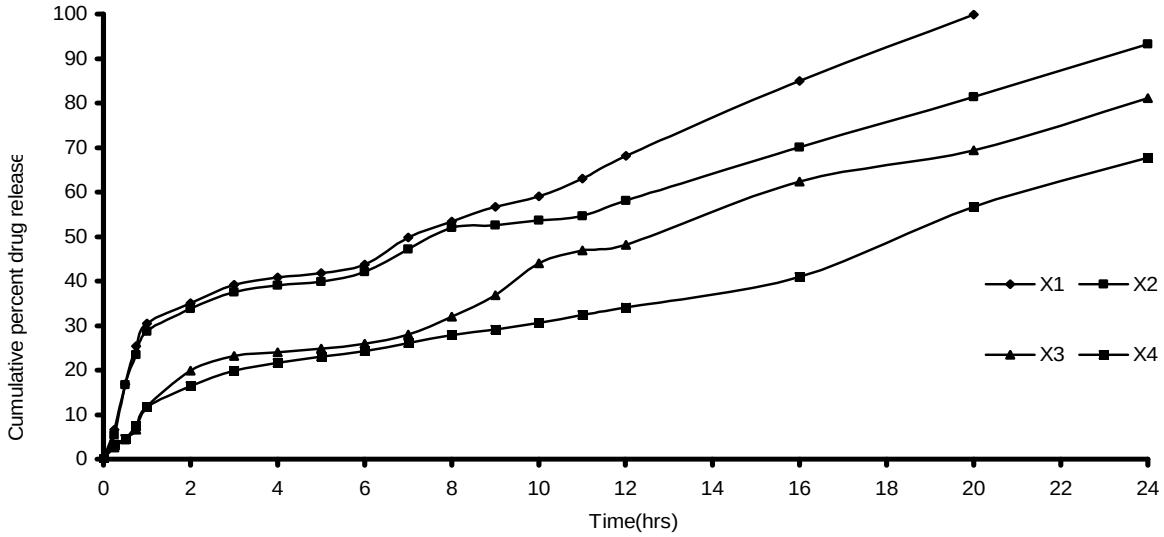

Fig 4: Effect of polymer level on *in-vitro* release of Mebeverine Hcl from XG matrix tablets

The *in vitro* release pattern of XG matrices as given in Fig 4 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 [18]. Swelling indices of XG also supported the results of *in vitro* drug release studies. 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.

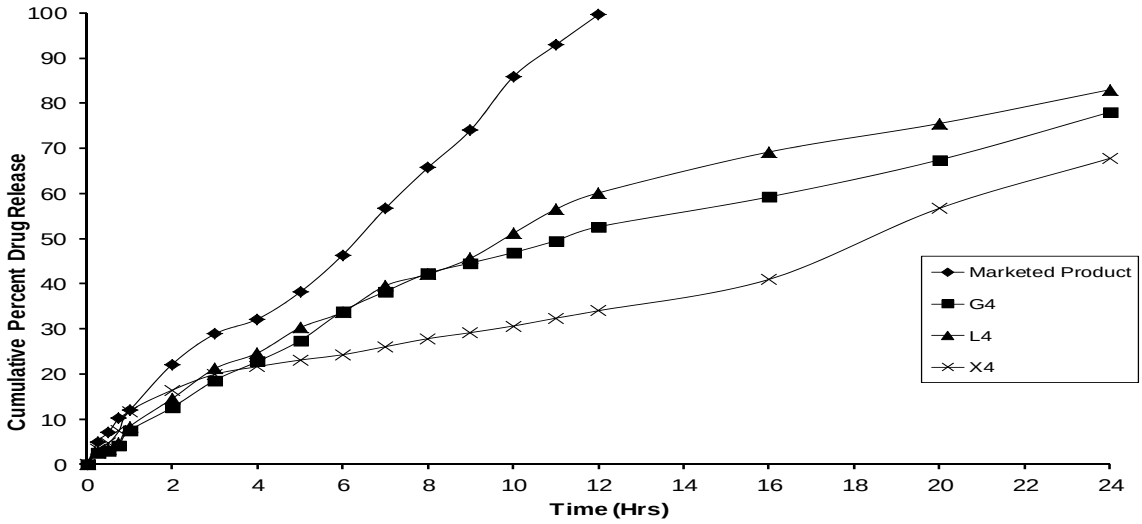

Fig 5: Comparison of *in-vitro* release study of optimized formulations with marketed capsule (Colospa SR 200mg capsule)

Comparison with marketed product: The release profiles of optimized matrix tablets of Mebeverine Hcl were compared with that of available marketed product (Colospa SR-200mg capsule). The optimized tablets prepared using GG (G4), LBG (L4) and XG (X4) 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 Hydrochloride.

Conclusion:

In conclusion, the drug release retarding ability of various gums investigated was in the order XG>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. 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.

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