International Journal of PharmTech Research
CODEN (USA): IJPRIF ISSN : 0974-4304
Vol.2, No.3, pp 1714-1722, July-Sept 2010

Studies on Design and In Vitro Evaluation of Compression-Coated Delivery Systems for Colon Targeting of Diclofenac Sodium

Chickpetty S. M.[1]* and Raga Baswaraj [2]

[1]Department of Pharmaceutics,K.R.E's Karnataka College of Pharmacy, Bidar-585403, Karnataka, India.

[2]Department of Bulk Drugs,K.R.E's Karnataka College of Pharmacy, Bidar-585403, Karnataka, India.

Corres author: sidhu_pharma77@yahoo.co.in

Abstract: Compression coating was one of the strategies used for delivering drugs to the colon. The present research work is aimed to develop colon targeted compression-coated delivery systems for diclofenac sodium by using different proportion of guar gum (GG) and locust bean gum (LBG) mixture in the ratio 1:1 in combination with hydroxy propyl methyl cellulose (HPMC) as a coating materials. Effect of proportion of GG-LBG mixture: HPMC ratio on percent of drug release in upper part of gastrointestinal tract and in the colon was studied on developed formulations. It was found that compression-coated formulation released 0 to 6.70 % of diclofenac sodium in the physiological environment of stomach and small intestine. The compression-coated formulation containing GG-LBG mixture:HPMC in the ratios 9:1, 8:2, 7:3, 6:4 and 5:5 released 35.84%, 47.62%, 78.61%, 94.82% and 98.03% of diclofenac sodium respectively in simulated colonic fluid indicating the susceptibility of gum mixture to the rat caecal contents. The results revealed that the tablets compression-coated with GG-LBG mixture and HPMC in the ratio 6:4 is most likely to provide targeting of diclofenac sodium for local action in the colon owing to their minimal drug release in physiological environment of stomach, and small intestine and more then 90% of drug release in the colon. The IR study indicates that the drug is intact in the formulation and no possibility of interaction between the diclofenac sodium and guar gum or locust bean gum or other formulation excipients.

Keywords: Diclofenac sodium, Locust bean gum, Guar gm, HPMC, Compression-coating and colon targeted drug delivery sytems.

Introduction

Dicolofenac sodium (DS) is a well known representative of non-steroidal anti-inflammatory drugs (NSAID's) widely used to control pain and inflammation of rheumatic and non-rheumatic origin [1]. NSAIDs also exert preventive effect against colon cancer that seems to be due to increased colon cell apoptosis[2]. The conventional DS tablets make the drug immediately available for absorption in upper gastrointestinal tract resulting local GI toxicity varying from minor gastric discomfort to ulceration and bleeding of the mucosa [3]. It is well documented that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa [4]. In addition rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times is required in maintenance therapy that influence patient compliance. Colon targeted controlled release formulation are thus warranted to promote patient compliance and to reduce upper GI toxicity to some extent. DS was selected as a model drug since it is well absorbed in the colon [5] and thus a formulation of DS with negligible to no drug release in upper part of GI tract and controlled release in colonic region would achieve effective therapeutic concentration of drug locally in colon. At the same time, such a formulation would minimize systemic or

upper GI tract side effects and colon specific release can be used for the treatment of widespread inflammatory bowel diseases.

Colon-specific drug delivery systems (CDDS) were developed to reduce side effects and achieve high local drug concentration at the afflicted site in the colon, hence optimal therapeutic effectiveness and good patient compliance [6-8]. It has been proved effective in treating colonic diseases such as inflammatory bowel diseases and colon cancer or improving absorption of protein or polypeptide drugs [9, 10]. A colonic drug delivery system is expected to protect the drug during the transit time in the gastrointestine and to allow its release only in the colon. The various approaches that have been studied for targeting orally administered drugs to the colon include use of pH-sensitive polymers [10,11], time-dependent dosage forms [12,13] and the use of carriers degraded by enzymes produced by colonic bacteria [14]. Of these approaches, the use of materials that are degraded by the colonic microflora has been found to be the most promising because of their site specificity[14,15]. These polymers shield the drug from the environment of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilatoion by micro-organisms or degradation by enzymes [16, 17].

Complicated by physiological variation in gastrointestinal conditions, many CDDS designs reported in literature have problems. The goal of CDDS design is to cut off precolon drug release and release drug at the afflicted site. Among the strategies, compression coated systems seem to be superior in preventing premature drug release in stomach and small intestine, while beginning to release the active agents at the proximal colon. On the other hand, the compression coated systems, usually in tablet form, is convenient to manufacture, and no special coating solvents or coating equipments are needed for coating process [9].

In the present research work, a model drug diclofenac sodium core tablets are compression-coated with a mixture of naturally occurring, biodegradable, inexpensive and non-toxic polysaccharide polymers guar gum and locust bean gum in combination with hydrophilic swellable polymer HPMC for colon–specific delivery. The effect GG-LBG mixture: HPMC ratio present in the coat formulation on the two critical release properties, drug release in upper part of gastrointestinal tract and drug release in target area or colon was investigated

Materials and Method

Materials

Diclofenac sodium obtained as a drug gift sample from Emcure pharmaceuticals Pvt. ltd., Pune. Locust bean gum was obtained as a gift sample from lucid colloids Pvt. Ltd., Mumbai, India. Guar gum obtained as a gift sample from Dabur research foundation, Ghaziabad, Gujarat. Hydroxy propyl methyl cellulose was purchased from Colorcon Asia Pvt. Ltd., Goa. Croos linked polyvinyl pyrollidone (Cross PVP) and spray dried lactose was obtained as a gift sample from M/s Arbindo pharma Ltd., Hyderabad., India. Starch, talc and magnesium stearate used for the preparation of tablets were purchased from commercial source Loba chemicals, Mumbai, India.

Preparation of fast disintegrating diclofenac sodium core tablets

Rapidly disintegrating diclofenac sodium core tablets (average weight 125mg) were prepared by direct compression technique. The composition of core tablet was given in table 1. A weighed quantity of drug, Cross PVP, lactose, talc and magnesium stearate required for 50 tablets of each batch was thoroughly mixed with mortar, and pestle and passed through the mesh (250µm) to ensure complete mixing. The uniformity of mixing was assessed by conducting content uniformity test on the sample of powder mixture. Quantity weighing 125mg was taken and compressed into tablets using 8mm round; flat and plain punches on a single station tablet punching machine (Cadmach, India).The quality control tests such as thickness, weight variation, hardness, disintegration, friability and dissolution were performed on the core tablets.

Preparation of diclofenac sodium compression-coated tablets

After confirming compliance with the above mentioned tests, the formulated core tablets were compression-coated with the different granular coat formulation of GG-LBG mixture and HPMC in different ratios with a coat weight of 400mg. The composition of compression-coat granular material was shown in table 2. For compression coating about 45% (180mg) of coat weight granular material was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre manually, which was then filled with the remainder 55% (220mg) of the coat granular material. The coating material was then compressed around the core tablet by using 11 mm round flat and plain punches.

Physical characterization of core and compression coated tablets

The developed core and compression-coated tablet formulations were studied for their physical properties like thickness, weight variation, hardness, friability and drug content uniformity using reported procedure [18]. For estimating weight variation, 20 tablets of each formulation were weighed using a single pan electronic balance (Elico, Mumbai, India).

The thickness of the tablet was measured by using a micrometer screw gauge. The hardness of five tablets was measured using Monsanto tablet hardness tester. Friability was determined on 10 tablets using Roche friability testing apparatus for 4 min at 25 rpm. The drug content studies were carried out to evaluate the amount of drug present in the core and compression coated tablets.

Estimation of drug content

The core and compression-coated tablets of diclofenac sodium were tested for their drug content. The 10 tablets were finely powdered, and quantity of the powder equivalent to 100 mg of diclofenac sodium was accurately weighed and transferred to 100 ml volumetric flasks containing 50 ml of phosphate buffer pH 6.8 and allowed to stand for 8 hour with intermittent shaking to ensure complete solubility of the drug. The solution then made up to 100ml volume with buffer pH 6.8 and mixed thoroughly. The solution were filtered, diluted and drug content was estimated by UV-spectrophotometer at 276nm (Shimadzu, Japan).

IR Studies

IR study was also carried out for pure drug diclofenac sodium, physical mixture of diclofenac sodium core tablet and the selected batch of compression-coated tablet formulation GLH4 to confirm absence of chemical interaction during tablet processing and storage. The IR spectrum was acquired in the range of 400-4000cm^{-1} with a resolution of 4cm-1. A representative IR spectras is shown in Figure 4.

In vitro drug release studies in artificial gastric and intestinal fluid

The ability of the prepared compression-coated tablet formulation to prevent or to remain intact with respect to time in the physiological environment of stomach and small intestine in pH conditions prevailing in stomach and small intestine was assessed by in vitro drug release in USP XXIII dissolution rate test apparatus (apparatus type 1,100rpm, 37±0.5ºC) for 2 h in pH 1.2 (900ml), as the average gastric emptying time is 2h, then the dissolution media is replaced with pH 7.4 phosphate buffer (900ml) and dissolution was continued for another 3 h as the usual small intestine transit time is 3-5 h and dissolution were continued in phosphate buffer pH 6.8 until completion of 24 h as the usual colon transit time is 20-30h. At the end of the time periods 5 ml sample were taken and analyzed for percentage of drug release by UV spectrophotometer at 276 nm (Shimadzu, Japan).

In vitro drug release studies in artificial rat caecal content fluid

The in vitro drug release studies were carried out using USP dissolution rate test apparatus (Apparatus 1, 100rpm, 37^0C) with slight modifications. A beaker (capacity 200ml) containing 150 ml of 4% rat cecal content medium was immersed in the phosphate buffer pH 6.8 maintained in 1000-ml vessel, which in turn, was in the water bath of the apparatus. The swollen formulation after completing the dissolution studies in 0.1M HCl (2 hr) and Phosphate buffer pH 7.4 (3 hr) were placed in the basket of the apparatus and immersed in the rat cecal content medium contained in 200 ml beaker. As the cecum is naturally anaerobic, the experiment was carried out with continuous supply of carbon- dioxide into the beaker. At the end of the time periods 3ml sample were withdrawn, centrifuged, diluted and analyzed for percentage of drug release by UV spectrophotometer at 276 nm.

Statistical Analysis

The Cumulative percent of diclofenac sodium released from optimized compression-coated tablet formulation GLH64 (n=3) in the dissolution medium at 24 h with and without rat cecal contents (control study) was compared, and the statistical significance was tested by using Student's *t* test. A value of $P< 0.05$ was considered statistically significant.

Results and Discussion

Dissolution of core tablets

Because outer coat of guar gum and locust bean gum mixture in combination with HPMC function as the controlling mechanism of diclofenac sodium release from compression coated tablet formulations, the core tablets were prepared with fast disintegration and dissolution characteristics. Tested in USP disintegration tester (Elico, India), the core tablets were found to disintegrate within 1min showing required fast disintegration characteristics. Because diclofenac sodium core tablets contains a super disintegrant cross PVP and water soluble directly compressible diluent spray dried lactose which might have contributed for such a fast disintegration of core tablets, over 90% of diclofenac sodium dissoluted in pH 1.2 buffer within 30 min. The fast disintegrating and dissolution of the core tablet prevent it from being the rate limiting factor.

Physical characterization of diclofenac sodium core tablets

The rapidly disintegrating diclofenac sodium core tablets were prepared by direct compression technique using cross PVP as a super disintegrant to aid fast disintegration of the core tablet and water soluble spray dried lactose as a direct compression aid. The compressional force was adjusted to give core tablets with approximately 3.0 kg/cm^2 hardness. The physical parameters for the core tablet formulations were found to be within the limits. Average weight of the core tablet was fixed at the lowest possible level (125mg) to accommodate maximum amount of coat material over the core tablet and the average

percentage deviation of core tablet was within the official limit. The core tablets were found to disintegrate within 50 sec showing required fast disintegration characteristics. The core tablet formulations passed the test for friability (<0.7%) and core tablets showed 99.26% of labeled amount of drug indicating uniformity of drug content in the core tablet formulation (Table 3).

Physical characterization of diclofenac sodium compression-coated tablets

The compression-coated tablet formulations were prepared according to the coat formula given in table 2.The compression-coated tablets of different formulations were subjected to various evaluation tests, such as thickness, uniformity of weight, drug content, hardness, friability and in vitro dissolution. All the formulations showed uniform thickness in a range of 5.11 to 5.21mm. In a weight variation test, the pharmacopoeia limit for the percentage deviation for the tablets of more than 250mg is ± 5%.The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percent of drug content was in the range of 97.47 % to 101.46 %. All the formulation showed a hardness value in the range of 4.88 to 5.43 kg/cm^2. Hardness of the tablet increases as the proportion of HPMC in the coat formulation increases. Tablet hardness is not an absolute indicator of strength .Another measure of tablet's strength is friability. The compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability of all the batches formulation was below 1% indicating that the friability is with in the limits. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specification for weight variation, drug content, hardness and friability.

IR Studies

The IR spectrums are shown in figure 4. The IR spectrum of pure drug diclofenac sodium (Fig.4A) shows a characteristic peaks at 3386 cm^{-1}due to N-H stretching frequency of secondary amine. The absorption bands at 1305 and 1282 cm^{-1} resulted from C-N stretching and the peaks at 1556 and 1574 cm^{-1} due to C=C stretching and C=O stretching of carboxylate group, respectively. The C-Cl stretching characteristic peak observed at 746 cm^{-1}. The IR spectra of diclofenac sodium core tablet (Fig.4B) and compression-coated formulation (Fig.4C) shows all the principal characteristic peaks related to diclofenac sodium without any change in their position, indicating no possibility of chemical interaction between the drug and formulation ingredients.

In vitro drug release studies

The present investigation was aimed to develop novel oral colon targeted compression-coated tablet formulations of diclofenac sodium for safe and effective therapy of rheumatoid arthritis and colitis by using GG,LBG and HPMC mixture as a coating materials. The coat formulation with various ratios of GG-LBG mixture and HPMC was prepared in the form of granules to impart both flowability and compressibility. The ability of compression-coated tablets of diclofenac sodium to remain intact in the physiological environment of stomach and small intestine was assessed by conducting in vitro drug release studies in 0.1N HCL for 2h and in phosphate buffer pH 7.4 for 3h and continued for another 19 h in phosphate buffer pH 6.8 with, and without rat caecal content in dissolution medium to assess the ability of the compression-coated tablets to release drug in the physiological environment of colon target area.

The percent of drug released from the formulation GLH1 compression coated with guar gum-locust bean gum mixture: HPMC in the ratio 9:1 were 0% at the end of 5 hour. This indicates that the coat formulation LBG91 controls premature drug release in upper part of gastrointestinal tract. To assess the integrity of the coat, drug release studies were carried out without addition of rat ceacal contents to pH 6.8 phosphate buffer solutions. At the of 24 h of dissolution study, the tablets coated with formulation GLH91 were intact and mean percent drug released was 29.54 % as shown in figure 1. The drug release was incomplete from the coat formulation GLH91 in the physiological environment of colon target area. This might be due to high proportion of GG-LBG mixture present in the outer coat shell and absence of rat caecal contents in the dissolution fluid phosphate buffer pH 6.8.

The percentage of diclofenac sodium released from compression coated formulation GLH82, HG73, GLH64 and GLH55 containing guar gum-locust bean gum mixture : HPMC in the ratios 8:2, 7:3, 6:4 and 5:5 was 0%, 0%, 2.24 % and 6.70% respectively after 5h of dissolution study. This indicates that GG-LBG: HPMC mixture as a compression coat is capable of minimizing the drug release in the physiological environment of stomach and small intestine. There was tight control of drug release in the physiological environment of stomach and small intestine. To assess the integrity / ability of coat the drug release studies were continued without addition of rat caecal content medium to phosphate buffer pH 6.8 for another 19 h. The mean percent of drug released at the end of 24 h of dissolution study from the formulation GLH82, GLH73, GLH64 and GLH55 was 33.36%, 38.01%,

40.49% and 52.99 % respectively. This indicates that the gums present in the coat is not degraded and until the coat is degraded, the gums will not permit the release of the remaining bulk of the drug present in the core in to the dissolution media.

The drug delivery system targeted to colon should not only protect the drug being released in the stomach and small intestine, but they also should release and sustain the drug release in the colon. Hence in vitro drug release studies were carried out in pH 6.8 phosphate buffer containing rat caecal contents. When the dissolution studies were carried out in the presence of 4% w/v of rat ceacal content medium, the percent drug released from diclofenac sodium core tablets compression-coated with coat formulation LGH91 was found to be 35.84 % up to 24 hours (Figure 1). The drug release was incomplete due to presence of high proportion of guar gum and locust bean gum mixture in the coat shell which might have not allowed its complete degradation during the testing period of 24 h. There was not much difference in the amount of diclofenac sodium released from the dissolution studies carried out in presence and absence of rat caecal content medium from the coat formulation GLH91. This clearly shows that the drug release is not due to complete action of colonic bacteria but due to mechanical diffusion of soluble drug from the formulation into dissolution fluid. Thus, it is evident that unless the coat is completely degraded by colonic bacteria, drug release may not increase. Hence, the proportion of guar gum-locust bean gum mixture was reduced in the coat formulation LGH82 and LGH73.

The percent of drug released from formulation LHG82 and GLH73 after 24 hr of dissolution study was 47.62% and 78.61% as shown in Figure 2 and the tablet coat was found to be degraded making way for the release of the drug from the core. The percent drug released from core tablets compression-coated with coat formulation LHG82 and GLH73 was found to increase in the lower part of GIT indicating the commencement of disruption of the hydrated gum coats due to degradation of the swollen gum mixture present in the coat. The proportion of gum mixture in the outer coat shell was further reduced in the coat formulation GLH64 and GLH55 with an objective to increase the percentage of drug release in the colon target area.

The tablets compression-coated with coat formulation GLH64 and GLH55, an increase in percent drug released was observed at 12 h and at the end of 24 hr of release study 94.82% and 98.03% of drug was released (Figure 3). The release of more then 90% of the drug from the coat formulation LGH64 and LGH55 indicates that the gum mixture present in the coat were completely degraded in the presence of rat caecal contents there by releasing the drug from the tablets in to rat caecal content dissolution medium. Since the proportion of guar gum and locust bean gum mixture of the coat formulation GLH64 and GLH55 was less as compared with coat formulation HG73. The coat might have completely hydrated and subsequently degraded by the caecal enzymes at a faster rate resulting in the release of 94.82% and 98.03% of drug from GLH64 and GLH55 coat formulation in the physiological environment of colon.

The study shows that as the proportion of gum mixture decreases in the coat formulations GLH73, GLH64 and GLH55 the percentage of drug release was increased in the physiological environment of colon. This might be due to fact that on coming in contact with dissolution fluid in first 5h of dissolution study, the coat hydrates and swells up. After 5h of dissolution study the hydrated and swollen coat increases the susceptibility of swollen polysaccharides gum content present in the coat to bacterial action thereby increased drug release in the colon target area.

Statistical Analysis

The percent of diclofenac sodium released from formulation GLH64 in the dissolution medium at 24 h with and without rat cecal contents (control study) were compared statistically using Student's *t* test. An increase in the amount of diclofenac sodium released was found significant ($P<0.005$) from GLH64 with rat cecal contents when compared to the in vitro drug release without rat cecal contents.

Conclusion

The objective of the present investigation is to design compression-coated tablets of diclofenac sodium for an effective and safe therapy of rheumatoid arthritis and colitis using guar gum and locust bean gum mixture as carriers. In conclusion, the core tablets compression-coated with GG-LBG mixture : HPMC as a coat material in the ratio 6:4 released only 2.24% of drug in the physiological environment of stomach and small intestine and released more then 90% of the drug in the target area i.e. physiological environment of colon .Thus, based on these results, the tablets containing optimum proportion of GG-LBG:HPMC mixture (6:4) is most likely to target diclofenac sodium to the colon with out being released significantly in stomach and small intestine.

Table 1: Composition of fast disintegrating diclofenac sodium core tablets

Ingredients	Quantity (mg) present in core formulation
Diclofenac sodium	100
Spray dried lactose	15
Cross linked PVP	6.25
Magnesium stearate	2.50
Talc	1.25
Total Weight	**125**

Table 2: Composition of granular coat formulation for diclofenac sodium core tablets

Ingredients	Quantity (mg) present in coat formulations				
	GLH91	**GLH82**	**GLH73**	**GLH64**	**GLH55**
Guar gum	157.5	140	122.5	105	87. 5
Locust bean gum	157.5	140	122.5	105	87. 5
HPMC (K_4M)	35	70	105	140	175
Starch (Added as paste)	40	40	40	40	40
Talc	6	6	6	6	6
Magnesium Stearate	4	4	4	4	4
GG:LBG ratio	1:1	1:1	1:1	1:1	1:1
GG-LBG Mix : HPMC	9:1	8:2	7:3	6:4	5:5
Coat Weight (mg)	400	400	400	400	400

Table 3: Physical characteristics of core and compression-coated tablets

Formulation Code	Thickness* (mm)	Hardness* (Kg/cm^2)	Friability (%)	Drug Content* (%)	Weight Variation (%)
Core	2.20±0.06	3.00 ± 0.14	0.637	99.26 ± 1.75	± 1.870
GLH91	5.11±0.13	4.88 ± 0.11	0.227	97.47 ± 1.07	± 2.032
GLH82	5.21±0.07	4.98 ± 0.75	0.284	97.56 ± 0.693	± 1.003
GLH73	5.20±0.10	5.03 ± 0.13	0.322	97.42 ± 0.96	± 3.098
GLH64	5.18±0.09	5.15 ± 0.17	0.209	101.46 ± 1.06	± 1.092
GLH55	5.18±0.12	5.43± 0.05	0.227	98.62 ± 1.35	± 1.074

*** All values are average of five determinations ± S.D.values**

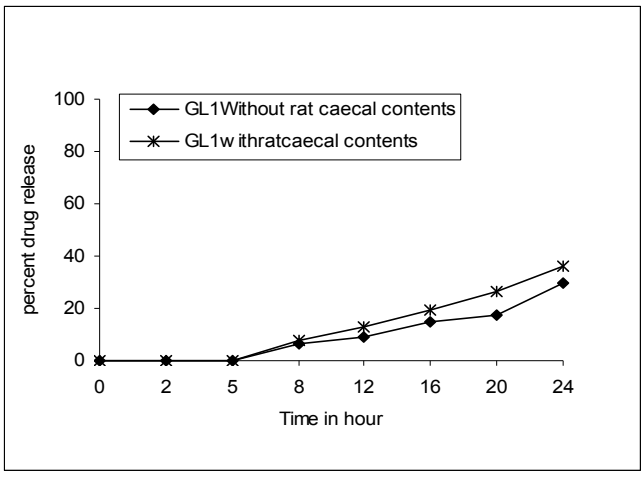

Figure 1: Release profile of diclofenac sodium from compression-coated tablet formulation GLH91containing GG-LBG mixture and HPMC in the ratio 9:1

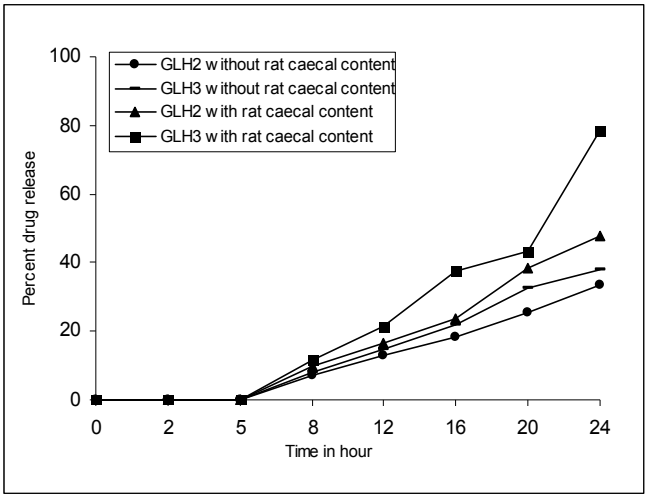

Figure 2: Release profile of diclofenac sodium from compression-coated tablet formulation LH82 and GLH73 containing GG-LBG mixture and HPMC in the ratio 8:2 and 7:3.

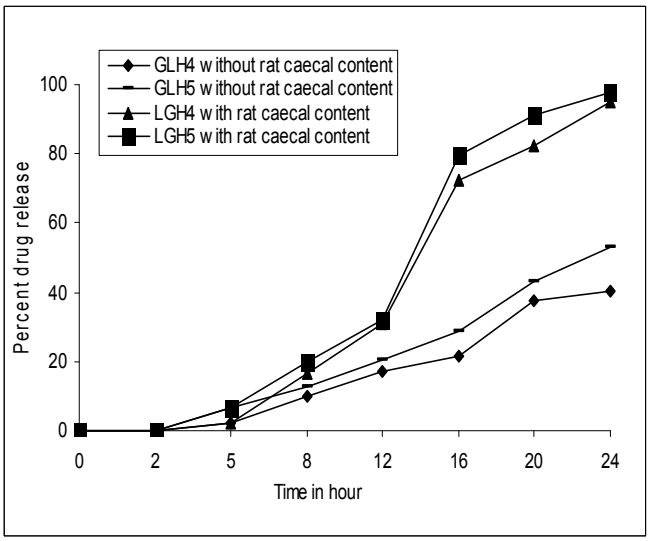

Figure 3: Release profile of diclofenac sodium from compression-coated tablet formulation GLH64 and GLH55 containing GG-LBG mixture and HPMC in the ratio 6:4 and 5:5.

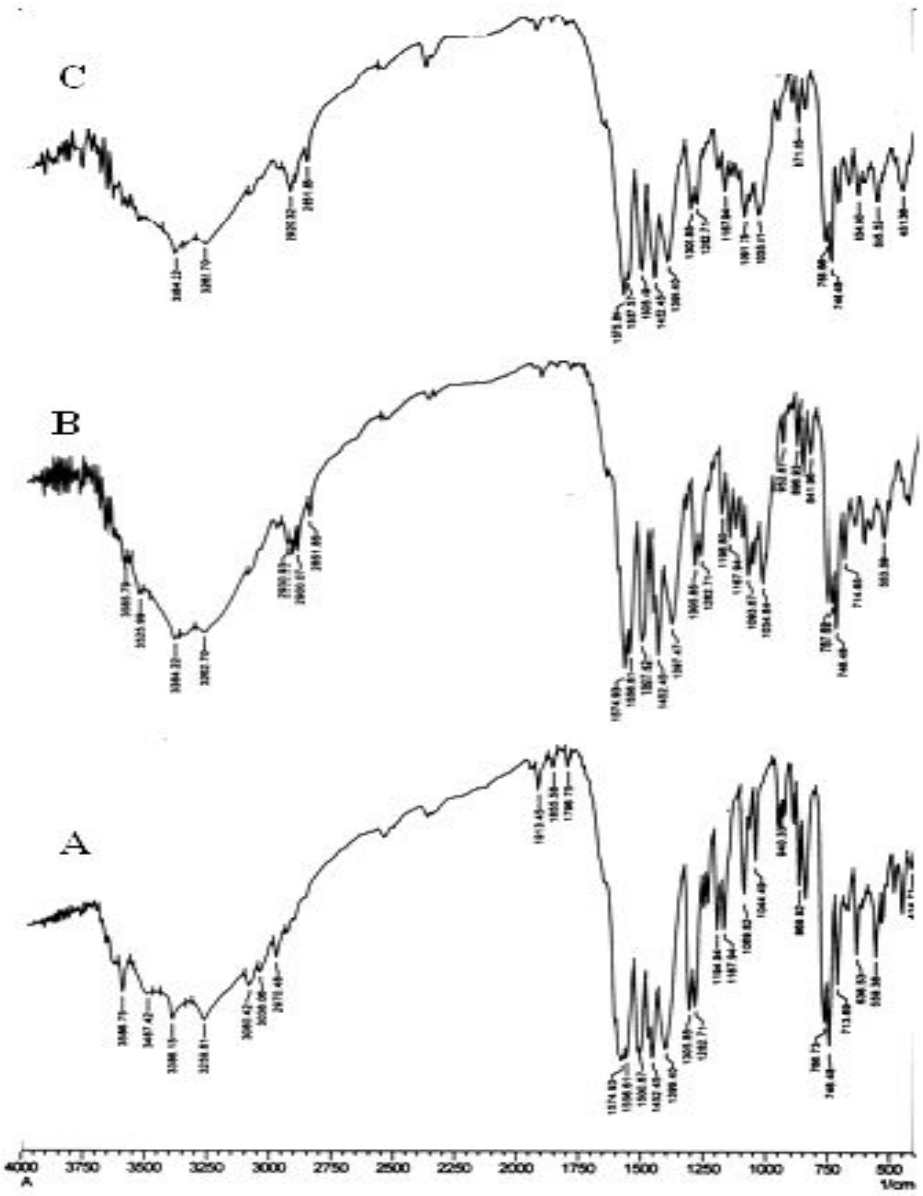

Figure 4: IR spectra of pure drug diclofenac sodium (A), powder core tablet formulation (B) and Compression-coated tablet formulation GLH64 (C).

Acknowledgement

The authors acknowledge the kind help received from Emcure pharmaceuticals, Pvt. Ltd., Pune, India for gift sample of diclofenac sodium. The authors gratefully acknowledge the Management, KRE's Karnataka College of pharmacy, Bidar-karnataka (India) for providing necessary facilities to carryout this research work.

References

1. Brogen R.N., Pakes G.E., Speight T.M., Avery G.S. Diclofenac sodium: A review of its pharmacological properties and therapeutic use in rheumatic diseases and pain of varying origin. Drugs., 1980, 20,24-48.
2. Clataynd S., Warner T.D., Breese E.J., Mitchell J. Relationship between endogenous colony stimulating factors and apoptosis in human colon cancer cells: role of cyclo-oxygenase inhibitors. Br. J pharmacol., 2001,134,1237-1244.
3. Carson J, Notis W.M, Orris E.S., Colonic ulceration and bleeding during diclofenac therapy. N Engl J Med., 1989, 323, 135-137.
4. Bjarnasson I, Fehily B, Smethurst P, Menziea I.S., Levi A.J., Importance of local versus systemic effects of non-steroidal anti-inflammatory drugs in increasing small intestinal permeability in man. Gut., 1991, 32,275-277.
5. Glieter C.H., Antonin K.H., BIECK P., Godbillon J, Schonlebr W, Malchow H. colonoscopy in the

investigation of drug absorption in healthy volunteers. Gastrointest Endosc.,1985, 31,71-73.
6. Friend, D. R. Colon-specific drug delivery. Adv. Drug Deliv.Rev.1991, 7,149-199.
7. Friend, D. R. New oral delivery systems for treatment of inflammatory bowel disease. Adv. Drug Deliv. Rev. 2005, 57, 247-265.
8. Lee, V.H.L.,; Mukherjee, S.K. Drug delivery-oral colon-specific. In Encyclopedia of pharmaceutical Technology. Marcel Dekker: New York, 2002, 871-885.
9. Krishniah, Y.S.R.; Satyanarayan, V.; Kumar B.D.; Karthikeyan, R.S. In vitro drug release studies on guar gum-based colon targeted oral drug delivery systems of 5-fluorouracil. Eur. J. Pharm. Sci. 2002, 16, 185-192.
10. Ashford, M.; Fell, J.; Atwood, D.; Woodhead, P. An in vitro investigation into suitability of pH-dependent polymers for colon targeting. Int. J. Pharm.1993, 91, 241-245.
11. Khan, M.Z. I., Prebeg,Z., Kurjakovic, N. A pH dependent colonv targeted oral drug delivery sytem using methacrylic acid copolymers I. Manipulation of drug release using Eudragit® L100 and Eudragit®S100 combination. J. Control.Release. 58:215-222.
12. Davis, S.S., Hardy, J, G.; Fara J.W.Transit of pharmaceutical dosage forms through the small intestine. Gut .1986, 27; 886-892.
13. Van den Mooter, g., Kinget, R.,. Oral colon specific delivery: a review. Drug Deliv. 1995, 2: 81-93
14. D. Sinha, V. R., Kumria, R. Binders for colon specific drug delivery: an invitro evaluation. Int. J. Pharm. 2002, 249; 23-31
15. Krishniah, Y.S.R.; Satyanarayan, S.; Rama Prasad, Y.V.; Narasimha Rao, S. Evaluation of guar gum as a compression coat for drug targeting to colon. Int. J. Pharm. 1998, 171, 137-146.
16. Potts, J.E., Clendigs R.A., Ackard W.B., and Wigisch W.D., The biodegradability of synthetic polymer. In: Guillet, J. (Ed), Polymer science and technology, Vol.3. Plenum Press, New York,PP.61-79,1973.
17. Huang, S.I., Bansleben,D.A., and Knox,J.R., Biodegradable polumers: Chymotrypsin degradation of low molecular weight poly (ester-urea) containing phenylalanine. J Appl Polym Sci,23:429-437,1979.
18. Govt of India Ministry of health and family welfare. The pharmacopoeia of India. Delhi, India: Controller of Publication; 2007.

*****