



Received on 11 June, 2015; received in revised form, 27 July, 2015; accepted, 03 October, 2015; published 01 December, 2015

STUDIES ON FORMULATION DEVELOPMENT AND IN VITRO EVALUATION OF CELECOXIB MATRIX TABLET CONTAINING COMBINATION OF EQUAL RATIO OF NATURAL GUMS GUARGUM AND CYCLODEXTRIN, AMYLOSE AND PECTIN FOR COLON SPECIFIC DRUG DELIVERY

P. Arulraj ^{*1,2}, V. Gopal ^{1,3}, G. Jeyabalan ¹, C. S. Kandasamy ^{1,2}, Sam Johnson J. Udaya Chander ² and R. Venkatanarayanan ²

Sunrise University ¹, Rajasthan, India.

Department of Pharmaceutical Biotechnology ², RVS College of Pharmaceutical Sciences, Coimbatore, Tamil Nadu, India.

College of Pharmacy ³, Mother Theresa Post Graduate & Research Institute of Health Sciences, Pondicherry, Tamil Nadu, India.

Keywords:

Celecoxib, Colon Targeted Drug Delivery, Matrix Tablet, Natural Polysaccharides

Correspondence to Author:

P. Arulraj

Associate Professor,


Department of Pharmaceutical Biotechnology, RVS College of Pharmaceutical Sciences, Suler - 402, Coimbatore, Tamil Nadu, India

E-mail: arulraj.p@rvsgroup.com

ABSTRACT: Backdrop: The design, development, formulation and *in vitro* evaluation of colon targeted drug delivery system with natural polysaccharides was studied with Guar gum, Cyclodextrin, Amylose and Pectin. Hence it motivated us to find the combined effect of the natural polysaccharides with Celecoxib matrix tablet for specific targeting to colon. **Process:** Celecoxib matrix tablet was prepared by drug with equal ratio of Guar gum+Cyclodextrin(A+B), Amylose+Pectin (C+D) were taken in the following equal ratio 1:0.2, 1:0.3 & 1:0.4 ratio of both gums, 2% of starch paste was added as binder. The micro crystalline cellulose was added to make the tablet total weight of 200mg. The formulations were coded as (A+B) EF1, (A+B) EF2, (A+B) EF3, (C+D) FF1, (C+D) FF2 and (C+D) FF3 respectively. The preformulation studies such as Bulk density (g/cm³), Tapped density (g/cm³), Compressibility index (%), Angle of repose, Average particle size (µm) were determined. **Outcome:** The formulated Celecoxib Matrix tablet was evaluated for its hardness, friability, weight variation, thickness and diameter. The discharge summary of the matrix tablet was carried out in Simulated Gastric Fluid (SGF), Simulated Intestinal Fluid (SIF), Simulated Colonic Fluid(SCF). The *in vitro* release profile of Celecoxib matrix tablet (A+B), (C+D) was found to be (EF2)88.4%, (FF2)95.3% correspondingly. **Ending:** It was found 1.5%, 6% of drug release was observed at 2 hrs, 4-8 hrs respectively with Simulated Gastric fluid and maximum of 95.3% of drug release was found after 24 hours of dissolution study. The above study suggests combined effect of amylose & pectin gives ceiling release for specific colon targeting especially for colon cancer.

INTRODUCTION: The colon, because of its position at the end of the alimentary canal, is not easy to access, and therefore the design of orally administered colonic delivery systems is complex.

The existing technique of 'targeting' drugs to the colon is achieved by formulating the desired drug molecules in a solid dosage form with natural polysaccharides. ¹⁻⁴ Factors influencing the transit point of pharmaceutical dosage forms in the various regions of the gastrointestinal tract appear to depend on diet, gastrointestinal motility, and physical activity of the person, fasted or fed state of the person. The transform in pH along the gastrointestinal tract was also used to develop colon specific drug delivery systems by applying coatings that were intact at low pH and dissolved at

<p>QUICK RESPONSE CODE</p> 	<p>DOI: 10.13040/IJPSR.0975-8232.6(12).5273-78</p> <hr/> <p>Article can be accessed online on: www.ijpsr.com</p> <hr/> <p>DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(12).5273-78</p>
-----------------------------------------------------------------------------------------------------------------------	---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

neutral pH.⁵ The pH of the colon is however; often lower than the pH of the small intestine, which in turn may be as high as 8 or 9, resulting in a too near the beginning discharge of a drug. Other reports conclude that pH is useful as a trigger for drug release in the colon. The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided into three main parts. These are the colon, the rectum and anal canal.⁶⁻¹⁰

Colonic microflora:

A large number of anaerobic and aerobic bacteria are present the entire length of the human GI tract. Over 400 distinct bacterial species have been found, 20-30% of which are of the genus bacteroids. The upper region of the GIT has a very small number of bacteria and predominantly consists of gram positive facultative bacteria. The rate of microbial growth is greatest in the proximal areas because of high concentration of energy source.¹¹⁻¹⁶ The metabolic activity of microflora can be modified by various factors such as age, GI disease, and intake of drug and fermentation of dietary residues.

Among the different approaches previously discussed, microflora activated systems appear to be more promising, since the abrupt increase of the bacterial population and associated enzymatic activity in the colon represents a non-continuous event, independent of the GI transit time. Microbially activated delivery systems for colon targeting are being developed to exploit the potential of the specific nature of diverse and luxuriant microflora associated with the colon compared to other parts of the GIT.¹⁷⁻²¹ This vast microflora in the colon survives by fermenting the various types of substrates that have been left undigested in the small intestine. The microflora of the human gastrointestinal tract consists of a coexisting mixture of aerobic, facultative anaerobic and strict anaerobic bacteria in a complex ecosystem.

It shows the presence of microorganisms along the GIT of different animals. These bacteria produce a wide range of enzymes, such as β -glucuronidase, β -xylosidase, α -arabinosidase, β -galactosidase,

nitroreductase, azoreductase, deaminase, urea hydroxylase. On account of these variations, it should not be a serious problem with interindividual enzyme activities in humans. On the other hand, the intraindividual variation arising from periodic consumption of certain foods and drugs has to be considered seriously if the microflora should be utilized. Diseases, or treatment with antibiotics, may influence the microbial flora.²²⁻²⁵ A disease resulting in decreased secretion of hydrochloric acid in the stomach, hypochlorhydria, may result in increased bacterial growth in the stomach. Some microorganisms were found to be suppressed after treatment with antibiotic.²⁶⁻³⁰

Aspirin and Celecoxib appear to decrease the danger of colorectal cancer in those at high risk. Celecoxib matrix tablet with natural polysaccharide was found to be effective in controlling the colon cancer. However, it is not recommended in those at average risk. There is tentative evidence for calcium supplementation but it is not sufficient to make a recommendation. Vitamin D intake and blood levels are associated with a lower risk of colon cancer.³¹⁻³⁶

MATERIALS AND METHODS:

Materials: The drug candidate Celecoxib was a gift sample from Torrent Pharma, Mumbai. Guar gum, Cyclodextrin, Amylose, Pectin, potassium chloride, hydrochloric acid, micro crystalline cellulose, magnesium stearate and talc were supplied by S.D. Fine chemicals Mumbai.

Methods:

The celecoxib matrix tablets were prepared by wet granulation method. Drug with equal ratio of Guar gum + Cyclodextrin (A+B), Amylose + Pectin(C+D) were taken in the following equal ratio 1:0.2, 1:0.3 & 1:0.4 ratio of both gums, 2% of starch paste was added as binder. The micro crystalline cellulose was added to make the tablet total weight of 200mg. Accurately weighed quantities of pre sieved drug and the gum material were mixed thoroughly, granulated and lubricated with mixture of talc and magnesium stearate.

The granules are now compressed by single tablet punch. The preformulation studies such as bulk

density, tapped density, compressibility index and angle of repose were carried out (**Table 1**). The matrix tablets were also evaluated for hardness, friability, weight variation, thickness and diameter as per the authenticated methods.

The weight variation was evaluated taking 20 tablets using an electronic balance (Afcoset, type ER182A). Tablet hardness was determined for 10 tablets using a Monsanto (standard type) tablet hardness tester. Friability was determined by testing 20 tablets (Campbell electronic friabilator) for 4 min at 25 rpm. Thickness and diameter of the tablet were measured using caliper scale (**Table 2**)

In-vitro Dissolution Studies:

Different matrix tablet formulations of Celecoxib were prepared by wet granulation technique using varying proportions of natural polysaccharides (Guar gum & cyclodextrin) and (amylase and pectin). Each formulation contains 100mg of Celecoxib. The formulations were coded as EF1, EF2, EF3, FF1, FF2, & FF3 by varying the natural polysaccharide percentage 20%, 30% & 40% respectively. The crystalline cellulose was included to adjust the tablet weight to 200mg. Accurately weighed quantities of pre-sieved drug and polymer were mixed thoroughly, granulated and lubricated with a mixture of talc and magnesium stearate. The granules thus obtained were compressed at a maximum force of 4000kg using 8mm round and slightly concave punches on 12-station rotary tablet punching machine - II MT (Remek, Ahmedabad, India). Three batches in each formulation containing 20 tablets were formulated. The matrix

tablets were evaluated for hardness (Tablet tester C-W WTDH 500N Thermionic, Campbell Electronics), friability (Thermionic, Campbell Electronics C – FT 10/20) and diameter as per the standard procedures.

Celecoxib matrix tablet release profile was determined using USP 23 dissolution test apparatus II (Paddle type). The dissolution test was performed using 900 ml of 0.1N HCL at 37 ± 0.5 °C with 50rpm. Aliquot (5ml) of the solution was withdrawn at pre determined time intervals (2 h) and replace with fresh dissolution medium. The aliquots were filtered through whatmann filter paper number 41. The absorbance of these solutions was measured on a double beam UV spectrophotometer (UV-1700 Shimadzu) at 252 nm with respect to blank dissolution media. The drug release profile was carried out in Simulated Gastric, Simulated Intestinal fluid and Simulated Colonic fluid to decide the best formulation (**Table 3**). A plot was made by taking the percentage of release Vs time (**Fig.1**).

RESULTS AND DISCUSSION: The matrix tablets of Celecoxib were prepared by wet granulation method and the tablets were subjected to its physical parameters and in vitro evaluation. The results obtained during the evaluation of the prepared matrix tablets were being tabulated below. Upon observing the results of *In vitro* drug release profile with SGF, SIF and SCF 30% of Amylose and pectin was found to give better release profile than guar gum and cyclodextrin combination.

TABLE 1: PREFORMULATION STUDIES OF A+B & C+D

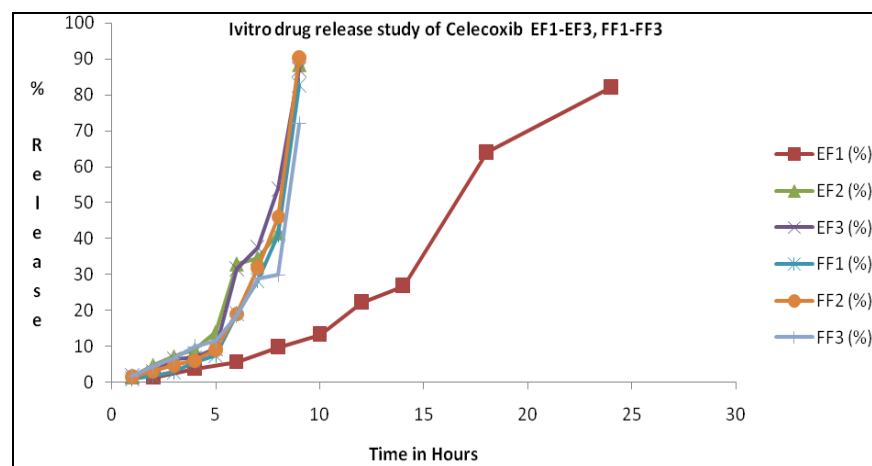
S.NO	PARAMETERS	Drug	EF1 (A+B)	EF2 (A+B)	EF3 (A+B)	FF1 (C+D)	FF2 (C+D)	FF3 (C+D)
1	Bulk density(g/cm ³)	0.33 ±0.007	0.71 ±0.015	0.75 ±0.02	0.78 ±0.089	0.68 ±0.105	0.72 ±0.230	0.74 ±0.610
2	Tapped density(g/cm ³)	0.58 ±0.008	0.63 ±0.02	0.66 ±0.13	0.72 ±0.012	0.67 ±0.02	0.77 ±0.01	0.84 ±0.17
3	Compressibility index (%)	39.62 ±0.11	10.81 ±0.32	13.12 ±0.26	14.40 ±0.10	12.56 ±0.53	13.87 ±0.01	16.76 ±0.19
4	Angle of repose	71 ⁰ ±3.5	32 ⁰ ±1.85	39 ⁰ ±3.12	47 ⁰ ±1.50	28 ⁰ ±0.45	35 ⁰ ±2.89	51 ⁰ ±0.59
5	Average particle size (µm)	16.62 ±0.5	610.0 ±3.62	675.9 ±1.28	743.0 ±0.74	599.7 ±2.46	630.0 ±3.00	721.4 ±0.92

TABLE 2: MATRIX TABLET EVALUATION

Formulation	Hardness (Kg/Cm ²)	Thickness (Mm)	Diameter (Mm)
EF1(A+B)	6.02 ± 0.30	4.02 ± 0.10	9.3 ± 0.06
EF2(A+B)	6.30 ± 0.09	4.00 ± 0.09	9.5 ± 0.04
EF3(A+B)	7.08 ± 0.11	4.04 ± 0.46	9.1 ± 0.10
FF1(C+D)	6.60 ± 0.65	4.03 ± 0.08	9.2 ± 0.65
FF2(C+D)	7.02 ± 0.72	4.06 ± 0.83	9.3 ± 0.81
FF3(C+D)	7.00 ± 0.03	4.06 ± 0.50	9.5 ± 0.09

TABLE 3: IN VITRO DRUG RELEASE PROFILE OF CELECOXIB (EF1, EF2, EF3, FF1, FF2, FF3)

S.NO	TIME (hr)	EF1 (%)	EF2 (%)	EF3 (%)	FF1 (%)	FF2 (%)	FF3 (%)
With Simulated Gastric Fluid							
1	2	1.4	1.6	1.8	1	1.7	1.9
With Simulated Intestinal Fluid							
2	4	3.9	4.8	2.9	1.9	3.5	4.5
3	6	5.7	7.2	6.5	3	4.7	6.8
4	8	9.9	9.1	6.8	5.5	6.2	10
With Simulated Colonic Fluid							
5	10	13.3	14	9.3	7.4	9.3	11.6
6	12	22.2	33	31.6	19.1	19	18.7
7	14	26.8	35.8	37.6	28.4	31.9	29.1
8	18	64	42.5	53.9	41	47	30
9	24	82.1	88.4	87.2	82.8	95.3	72

**FIG. 1: IN VITRO DRUG RELEASE PROFILE OF CELECOXIB (EF1, EF2, EF3, FF1, FF2, FF3)**

SUMMARY AND CONCLUSION: Matrix tablets of Celecoxib with varying Concentration of Guar gum and Cyclodextrin were formulated. Invitro dissolution studies shows that the formulation of Celecoxib matrix tablet with guar gum and cyclodextrin as the polysaccharide (EF2) shows good release behavior in colon (88.4%) and restricts release of 38% release in stomach and 19.6% in intestine as compare to other formulations. This study confirms that guar gum and cyclodextrin cannot act as good carrier in the form of matrix tablet for Celecoxib when compared with Amylose and Pectin to deliver it in colon FF2 (95.3). It was found 1.5% of drug release was

observed at 2 hrs with Simulated Gastric fluid, 6% of drug release was found at 4-8 hrs with Simulated Intestinal fluid and maximum of 95.3% of drug release was found after 24 hours of dissolution study.

ACKNOWLEDGEMENTS: I am incredibly grateful to Dr. K.V. Kupusamy, Chairman RVS Educational Trust, Mr. K. Senthil Ganesh, Managing Trustee, RVS Educational trust, Dr. H. Mohamed Mubarak, Secretary, RVS Educational trust, Mr. Natrajan, Chief Executive of RVS Educational Trust, Dr. R. Venkatanarayanan, Principal, RVSCOPS, Dr. R. Manavalan, Research

Director, RVSCOPS, Teachers, Students of RVS College of Pharmaceutical Sciences, Sulur, Coimbatore, Chancellor, Pro Chancellor, Vice Chancellor of Sunrise University, Rajasthan for providing support and Prof. Dr. V. Gopal, Principal, College of Pharmacy, Mother Theresa Post Graduate & Research Institute of Health Sciences, Pondicherry, Dr. G. Jeyabalan, Principal, Alwar College of Pharmacy, Alwar, Rajasthan for their valuable guidance during this research work.

REFERENCES:

- Tomolin, J., Taylor, J.S., Read, N.W. The effect of mixed faecal bacteria on a selection of viscous polysaccharide *in vitro*. *Nutr. Rep. Int.*, 1989; 39:121–135.
- Bayliss, C.E., Houston, A.P. Degradation of guar gum by faecal bacteria. *Appl. Environ. Microbiol.*, 1986; 48:626–632.
- Macfarlane, G.T., Hay, S., Macfarlane, S., Gibson, G.R. Effect of different carbohydrates on growth polysaccharidases and glycosidase production of *Bacteroides ovatus* in batch and continuous culture. *J. Appl. Bacteriol.*, 1990; 68:179–187.
- Chourasia, M.K. and Jain, S.K. Potential of guar gum microspheres for target specific drug release to colon. *Journal of Drug Targeting*, 2004;b2 (4)1–8.
- Goldstein, A.M., Alter, E.N., and Seaman, J.K. Guar gum. In *Oral Colon-Specific Drug Delivery and Their Derivatives*, ed. R. L. Whistler, 1992; 26:1-43. NY, Plenum Press.
- Johnson, J.C., and Gee, J.M. Effect of gel forming gum on the intestinal unstirred layer and sugar transport *in vitro*. *Gut*, 1981; 22:398–403.
- Tomlin, B.J., Read, N.W., Edwards, C.A., Duerden, B.J. The degradation of guar gum by fecal incubation system. *Brit. J. Nutr.*, 1986; 55:481–486.
- Sinha, V.R., Kumria, R. Polysaccharides in colon-specific drug delivery. *Int. J. Pharm.*, 2001; 224:19–38.
- Friend, D.R. New oral delivery systems for treatment of inflammatory bowel disease. *Advanced Drug Delivery Reviews*, 2005; 57:247– 265.
- Antenucci, R., Palmer, J.K. Enzymatic degradation of α and β -cyclodextrins by bacteroids of the human colon. *J. Agric. Food Chem.* 1984; 32:1316–1321.
- Gerloczy, A., Fonagy, A., Keresztes, P., Perlaky, L., and Szejtli, J. Absorption, distribution, excretion and metabolism of orally administered ^{14}C - β -cyclodextrin in rat. *Arzneim Forsch/Drug Res.*, 1985; 35:1042–1047.
- Flourie, B., Molis, C., Achour, L., Dupas, H., Hatat, C., Rambaud, J. C. Fate of β -cyclodextrin in the human intestine. *J. Nutr.*, 1993; 123:676–680.
- Uekama, K., Hiramaya, F., Irie, T. Pharmaceutical uses of cyclodextrin derivatives. In *High Performance Biomaterials*, ed. M. Szycher, 1991; 789–786. Lancaster, PA, Technomic Publishing.
- Stella, V.J., Rajewski, R.A. Cyclodextrins, their future in drug formulation and delivery. *Pharm. Res.*, 1997; 14:556–567.
- Karunaratne, D.N., Farmer, S., Hancock, R.E.W. Synthesis of bulky beta-lactams for inhibition of cell surface beta-lactamase activity. *Bioconjug. Chem.*, 1993; 4:434–439.
- Tanaka, H., Kominato, K., Yamamoto, R. Synthesis of doxorubicin cyclodextrin conjugates. *J. Antibiot.*, 1994; 47:1025–1029.
- Coates, J. H., Easton, C. J., Fryer, N. L., Lincolin, S. F. Complementary diastereo selectivity in the synthesis and hydrolysis of acylated cyclodextrins. *Chem. Lett.*, 1994; 1:1153–1156.
- Minami, K., Hiramaya, F., Uekama, K. Colon-specific drug delivery based on a cyclodextrin prodrug, release behaviour of biphenyl acetic acid from its cyclodextrin conjugates in rat intestinal tracts after oral administration. *J. Pharm. Sci.*, 1998; 87:715–720.
- Uekama, K., Minami, K., Hirayama, F. 6-A-O-[(4-biphenyl)acetyl]- α -, β - and γ -cyclodextrins and 6A-deoxy-6A-[[[(4-biphenyl)acetyl]amino]- α -, β - and γ -cyclodextrins, potential prodrugs for colon-specific delivery. *J. Med. Chem.*, 1997; 40:2755–2761.
- Hiramaya, F., Minami, K., and Uekama, K., In vitro evaluation of biphenyl acetic acid- β -cyclodextrin conjugates as colon-targeting prodrugs, Drug release behaviour in rat biological media. *J Pharm Pharmacol*, 1996; 48:27-31.
- Yano, H., Hirayama, F., Kamada, M., Arima, H., Uekama, K., Uekama, K. Colon-specific delivery of prednisolone-appended α -cyclodextrin conjugate, alleviation of systemic side effect after oral administration. *J. Control. Rel.*, 2002; 79:103–112.
- Ciftci, K. Alternative approaches to the treatment of colon cancer. *Eur. J. Pharm. Biopharm.*, 1996; 42:160–170.
- Hardy, J.G., Wilson, C.G., and Wood, E. Drug delivery to the proximal colon. *J. Pharm. Pharmacol.*, 1985; 37: 874.
- Hollander, D. Intestinal Permeability, leaky gut, and intestinal disorders. *Curr Gastroenterol Rep*, 1999; 1: (5), 410-416.
- Ryde, E.M. Low molecular weight azo compounds, in *Oral Colon-Specific Drug Delivery*, Friend, D. R. Ed, CRC Press, Boca Raton, 1992; 143.
- Gruber, P., Longer, M.A., and Robinson, J.R. Some biological issues in oral, controlled drug delivery. *Adv. Drug Del. Rev.*, 1987; 1:1.
- Ryde, E.M. Low molecular weight azo compounds, in *Oral Colon-Specific Drug Delivery*, Friend, D. R. Ed, CRC Press, Boca Raton, 1992; (b)143.
- Arulraj P, Saraswathy R, Gopal V, Nair R, Kandasamy C S, Venkatanarayanan R. Microbial approach of rat colonic Microflora – A dangerous stringent anaerobe for targeting to colon. *International Journal of Research in Ayurveda & Pharmacy*, 2010; 1:1135-139
- Arulraj P, Saraswathy R, Nair Chandini R, Gopal V, Venkatanarayanan R. Studies on formulation and invitro evaluation of diclofenac sodium and biodegradation by rat's ceacal Microflora for colon targeted drug delivery system. *International Journal Research in Ayurveda & Pharmacy*, 2010; 1:2, 408-413
- Arulraj P, Saraswathy R, Chandini Nair R, B S Nath., VKSM Subramanyam M, Venkatanarayanan R. Isolation and characterization of rat colonic Microflora for targeting to colon. *International Journal of Pharma and BioSciences*. 2010; 1:4, 597-600
- Cooper K, Squires, H, Carroll, C, Papaioannou, D, Booth, A, Logan, RF, Maguire, C, Hind, D, Tappenden, P."Chemoprevention of colorectal cancer: systematic review and economic evaluation". *Health technology assessment (Winchester, England)* 2010; 14 (32): 1–206.
- Agency for Healthcare Research and Quality.

- "Aspirin or Nonsteroidal Anti-inflammatory Drugs for the Primary Prevention of Colorectal Cancer". United States Department of Health & Human Services. 2010/2011
33. Weingarten MA, Zalmanovici, A, Yaphe, J Weingarten, Michael Asher MA, ed. "Dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps". Cochrane database of systematic reviews (Online) 2008; (1)
34. Ma Y, Zhang, P, Wang, F, Yang, J, Liu, Z, Qin, H "Association between vitamin D and risk of colorectal cancer: a systematic review of prospective studies". Journal of clinical oncology: official journal of the American Society of Clinical Oncology 2011; 29 (28): 3775–82.
35. Yin L, Grandi, N, Raum, E, Haug, U, Arndt, V, Brenner, H (Jul 2011). "Meta-analysis: Serum vitamin D and colorectal adenoma risk". Preventive medicine 53. 2011;(1–2): 10
36. Arulraj P, Gopal V, Jeyabalan G, Kandasamy C S, Sam Johnson Udaya Chander, Venkatanarayanan R. Studies on formulation development and invitro evaluation of Celecoxib matrix tablet containing Amylose and pectin as natural polysaccharides for colon specific drug delivery. World journal of Pharmacy and Pharmaceutical Sciences,. 2015; 4:7, 1247-52
37. Arulraj P, Gopal V, Jeyabalan G, Kandasamy C S, Sam Johnson Udaya Chander J, Venkatanarayanan R. Natural polysaccharides for specific targeting to colon- an assessment. European journal of biomedical and Pharmaceutical Sciences,2015;4 :2 in press

How to cite this article:

Arulraj P, Gopal V, Jeyabalan G, Kandasamy CS, Sam Johnson UCJ and Venkatanarayanan R: Studies on Formulation Development and *In Vitro* Evaluation of Celecoxib Matrix Tablet Containing Combination of Equal Ratio of Natural Gums Guar gum and Cyclodextrin, Amylose and Pectin for Colon Specific Drug Delivery. Int J Pharm Sci Res 2015; 6(12): 5273-78.doi: 10.13040/IJPSR.0975-8232.6(12).5273-78.

All © 2013 are reserved by International Journal of Pharmaceutical Sciences and Research. This Journal licensed under a Creative Commons Attribution-NonCommercial-ShareAlike 3.0 Unported License.

This article can be downloaded to **ANDROID OS** based mobile. Scan QR Code using Code/Bar Scanner from your mobile. (Scanners are available on Google Playstore)