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Ternary Blends of some Hydrophilic and Hydrophobic Polymers in Colon Targeted Delivery of Metronidazole

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Abstract

Matrix tablets were prepared using blends of xanthan gum (XG), Guar gum (GG) and ethylcellulose (EC). The polymers were combined using six different ratios; 1:1:1, 1:2:1, 1:2:2, 2:2:1, 2:1:2 and 2:1:1 to produce formulations XG1GG1EC1, XG1GG2EC1, XG1GG2EC2, XG2GG2EC1. XG2GG1EC2 and XG2GG1EC1 respectively. Metronidazole was used as the model drug. The ability of the prepared matrices to target drug release predominantly at the colon under the influence of colonic bacteria was evaluated using the dissolution medium containing 4 % caecal content. Our results show that, optimum drug release was observed with formulations XG2GG2EC1 and XG2GG1EC1 with Cmax of 60 and 76 % respectively. Significant difference ($P<0.05$) was observed between drug release in dissolution medium with and without rat caecal contents for the batches of Metronidazole tablets. Formulations (XG2GG2EC1 and XG2GG1EC1) followed Higuchi square roots kinetics (r2 =0.9942) via fickian diffusion ($n < 0.45$) and Korsemeyer model (r2 = 0.9939) via non – fickian diffusion ($n > 0.45$) respectively.

Keywords: matrix.guar, xanthan, ethylcellulose, metronidazole, colon delivery

Introduction

Colon-specific drug delivery has gained increased importance in the delivery of drugs for the treatment of local diseases associated with the colon, such as Crohn's disease, ulcerative colitis, colorectal cancer and amoebiasis [1]

Metronidazole, the drug of choice for intestinal amoebiasis, has to be delivered to the colon for its effective action against .Entamoeba histolytica. Metronidazole is rapidly and completely absorbed after oral administration of conventional tablet dosage forms. Although these tablets provide a minimal amount of metronidazole for local action in the colon which is still effective in relief of amoebiasis, undesirable systemic side effects occur upon their administration [2]. Hence, the need for colon targeted delivery using biodegradable and other suitable polymers.

Although, several researchers [3-9]have reported the suitability of ethylcellulose, guar and xanthan gums in colon drug delivery, there is dearth of information on the blends of these polymers in colon targeting.

Literature search reveals that, these three polymers have never been investigated as blends for target delivery of metronidazole to the colon. The aim of the present study therefore, was to investigate the development of various metronidazole colon-specific delivery systems that could be formulated by using single and ternary blends of ethylcellulose, guar and xanthan gums.

Materials and methods

Metronidazole, Ethylcellulose, Guar gum and xanthan gum were all purchased from Sigma Aldrich, USA .Lactose monohydrate and magnesium stearate were procured from BDH, England. All other chemicals used were of analytical grade.

Methods

Preparation of metronidazole matrix tablets

The polymers (Xanthan gum, Guar gum and ethylcellulose) were included in the formulation in various proportions. The drug was geometrically blended with sufficient quantity of lactose and the polymer as stated in Table 1, using pestle and mortar. Mixing was maintained for 10 minutes and the powder mixtures stored in well-closed specimen bottles.

Direct compression method was used for making the tablets. Before each compression, the die (9.5 mm in diameter) and flat faced punches were lubricated with a 1 % w/v dispersion of magnesium stearate in chloroform. Compression was achieved using a single punch tableting machine (THP Shangai, Tianxiang and Chentai Pharmaceutical Machinery Co.Ltd. China) fitted with flat-faced punches and compressed to a target weight of 500 ± 10 mg.

Table 1: Composition of Metronidazole matrix tablets

FORMULATIONS	INGREDIENTS				
	API(mg)	GG	XG	EC	LACTOSE
XG1GG1EC1	200	20	20	20	240
XG1GG2EC1	200	15	30	15	240
XG1GG2EC2	200	12	24	24	240
XG2GG2EC1	200	24	24	12	240
XG2GG1EC2	200	24	12	24	240
XG2GG1EC1	200	30	15	15	240

Key: XG = Xanthan gum, GG = Guar gum, API = Active Pharmaceutical Ingredient GG1 = 10 % Guar Gum, XG1 = 10 % Xanthan gum, EC1 = 10 % Ethylcellulose

Each drug compacts were stored in airtight specimen bottles and allowed to equilibrate 24 hours before further evaluations.

Evaluation of powder mixtures

The powder mixtures were evaluated for angle of repose [10] bulk density [11], tapped density, compressibility index and hausner ratio [12] for micromeritic properties.

Evaluation of tablets

Tablets were evaluated for thickness and hardness [13] as well as friability [14] and weight variation [15] using standard methods. Content uniformity was evaluated using the method described by the Indian Pharmacopoeia [16].

Preparation of rat cecal content medium

The method of Emeje et al [22] was adopted for this study. Briefly, Wistar rats weighing 150-200g and maintained on a normal diet (soaked gram) were used. Forty-five minutes before the commencement of drug release studies, seven rats were killed by spinal traction. The abdomen were opened, the cecal were traced, ligated at both the ends, dissected, and immediately transferred into pH 7.4 buffer previously bubbled with nitrogen. The cecal bags were opened, their contents were individually weighed, pooled, and suspended in the buffer continuously bubbled with carbon dioxide. These were finally added to the dissolution media to give a final cecal dilution of 4%w/v, respectively. All the above procedures were carried out under carbon dioxide in order to maintain anaerobic conditions. In carrying out this study, ethical guidelines were adhered to in accordance with the "Principles of Laboratory Animal Care" [25] and institutional standard operating procedures after obtaining permission from the institutional animal ethics committee.

In-vitro drug release studies

The ability of matrix tablets of metronidazole to remain intact in the physiological environment of stomach and small intestine was assessed by mimicking mouth to colon transit. Drug release studies were carried out using USP XXIII dissolution apparatus (Apparatus 1, 100 rpm, 37.5oC) in 500 ml 0.1 N HCl for 2 h as the average gastric emptying time is 2h.. The dissolution medium was replaced with 500 mL of pH 7.4 phosphate buffer saline (PBS) and the dissolution was continued for 24 h. A 5 ml of the sample was taken at the specified time period (1 h, 2 h, 4 h, 5 h, 8 h, 10 h, 12 h, and 16 h) and analyzed at 250nm for Metronidazole using a Shimadu UV Spectrophotometer (Shimadu, Japan with . A 5 ml volume of filtered, fresh dissolution medium was added to make the volume after each sample withdrawal [17].

The susceptibility of the matrix tablets to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 100 mL of simulated colonic fluids (pH 6.8 phosphate buffered saline containing 4 % w/v of caecal contents of rats treated) (18). The drug release studies were carried out in USP dissolution test apparatus (apparatus 1, 100 rpm, 37 oC) with slight modification. A beaker (capacity 150 mL) containing 100 mL of dissolution medium was immersed in the water contained in the 1000 mL vessel, which in turn, was the water bath of the apparatus. The tablets, after completing the dissolution study in 0.1 M HCl (2 h) and pH-7.4 phosphate buffer (3 h) were placed in the baskets of the apparatus and immersed in the dissolution medium containing rat caecal contents. The release studies were carried out up to 24 h and 1 ml samples were withdrawn at specified time intervals (6 h, 8 h, 10 h, 12 h, 16 h and 24 h) without a pre-filter and replaced with 1 ml of fresh phosphate buffer. Samples withdrawn were analyzed for drug content at 250 nm.

Drug release kinetics

To analyze the mechanism of drug release rate kinetics, the results of invitro release profile were plotted in various kinetic models like zero order, first order, Higuchi model and korsmeyer – peppas [19].

Results and Discussions

The powder mixtures of all the formulations were evaluated for angle of repose, bulk density, tapped density, and Hausner ratio. The angle of repose was found to be 35 – 41o. The bulk and tapped densities were found to be in the range of 0.522- 0.571 gm/cc and 0.750 -0.833 gm/cc respectively. The Hausner ratio was found to be 1.3 to 1.5 indicating moderate flow characters of the powder mixtures (table-2).

Table 2: Evaluation of Metronidazole matrix powder mix

parameters	Formulations					
	XG1GG1EC1	XG1GG2EC1	XG1GG2EC2	XG2GG2EC1	XG2GG1EC2	XG2GG1EC1
Angle of repose (0)	39.81	38.81	41.14	37.64	39.81	35.07
Bulk density (gm/cc)	0.571	0.545	0.522	0.545	0.536	0.545
Tapped density (gm/cc)	0.769	0.769	0.750	0.769	0.750	0.833
Hausner ratio	1.347	1.411	1.437	1.411	1.400	1.530

The hardness of the tablets for all the formulations was in the range of 4.4 - 4.7 kg/cm2. The uniformity weight of 20 tablets of all the formulations was within 5% deviation. The friability of all the formulation was less than 1 %. Drug content of all the formulations were found to be in the range of 98 to 99 % (table-3). All the results are within the prescribed limits [13].

Table 3: Evaluation of Metronidazole matrix tablets

parameters	Formulations					
	XG1GG1EC1	XG1GG2EC1	XG1GG2EC2	XG2GG2EC1	XG2GG1EC2	XG2GG1EC1
Hardness (kg/cm2)	4.6±0.44	4.5±0.44	4.4±0.39	4.6±0.39	4.7±0.47	4.7±0.58
Weight (mg)	496.9±4.53	497.8±5.61	496.6±4.22	496.2±3.99	497.7±5.85	496.8±5.30
Friability	0.4	0.8	0.8	0.4	0.8	0.8
Drug content (%)	99	98	99.6	98	99	98.75
Thickness (mm)	4.91±0.05	4.97±0.02	4.95±0.04	4.97±0.03	4.98±0.07	4.97±0.02
Diameter (mm)	12.63±0.02	12.65±0.02	12.66±0.01	12.69±0.02	12.68±0.01	12.69±0.01

Dissolution profiles of Tablets

The time taken for 50% and 70% of the drug to be released (T50% and T70%) respectively and the maximum cumulative amount of drug release (Cmax) were used to characterize the release profiles of the matrix tablets (Tables 4).All the batches except batches XG2GG2EC1 and XG2GG1EC1 were not able to retard the release of the drugs beyond 5h.During the in vitro drug release studies, all formulations were observed for physical integrity at different time intervals. All the formulations swelled and the outer layer of most of the tablets appeared to be hydrated after being placed in the dissolution medium, with progressive increase in the size of these hydrated matrices. There was also gel formation followed by gradual loss of integrity over a period, resulting from hydrodynamic stress induced by the dissolution apparatus. The quick hydration and subsequent gel formation is a foremost and important property of an excipient intended for use in sustained released formulations [18].

Table 4: Some Release parameters of Metronidazole Tablets

parameters	Formulations					
	XG1GG1EC1	XG1GG2EC1	XG1GG2EC2	XG2GG2EC1	XG2GG1EC2	XG2GG1EC1
T50 (h)	2.40	2.80	1.75	10.70	2.90	6.35
T70 (h)	4.80	4.50	3.90	-	4.60	11.40
Cmax (%)	81.00	84.00	89.00	60.00	85.00	76.00

Table 5: Kinetics and mechanism of release for formulated metronidazole matrix tablets

formulation,	Zero - order	First – order	Higuchi	Korsmeyer(n)
XG2GG2EC1	0.9717	0.9897	0.9940	0.9928 (0.44)
XG2GG1EC1	0.9574	0.9860	0.9889	0.9939(0.46)

For matrices containing higher percentage of Xanthan gum (XG2GG1EC1 and XG2GG1EC2), there was an initial burst of Xanthan gum erosion from the matrices in the acidic pH, thereafter the erosion slowed considerably. Presence of Xanthan gum in combination with Guar gum in the tablets retarded the initial release of drugs from the tablets due to high swelling, which made them more vulnerable to digestion by the microbial enzymes in the colon (4). The Cmax values for XG1GG1EC1, XG1GG2EC1,

XG1GG2EC2, XG2GG2EC1. XG2GG1EC2 and XG2GG1EC1 were 81%, 84.5%, 89 %, 60%, 85 % and 76 % respectively. There was significant difference (P<0.05) in the release profiles of XG2GG2EC1 and the other formulations (XG1GG1EC1, XG1GG2EC1, XG1GG2EC2. XG2GG1EC2 and XG2GG1EC1), which had no significant difference (P > 0.05) in their release profiles. Formulation with higher proportion of xanthan gum displayed higher retardation ability [23, 24].

Drug release studies with and without rat caecal content

The susceptibility of Guar gum, Xanthan gum and ethylcellulose, to the enzymatic action of colonic bacteria, was assessed by continuing the drug release studies in rat caecal content medium for 24 h after 5 h of testing in simulated gastric and intestinal fluids. Figure 2 shows that the presence of rat caecal content in the dissolution medium resulted in a significant increase in drug release, when compared with control (P < 0.05). The cumulative percent of drug release from drug released after 24 h from XG2GG2EC1 and XG2GG1EC1 increased from 71.5% and 79.5% in the absence of rat caecal contents (control) to 89 % and 90 % (Figure 2) in the presence of rat caecal matter, respectively, indicating that polysaccharide metabolizing enzyme is present in the rat caecal contents. The implication is that the polymers used in the formulations were susceptible to the enzymatic action of colonic bacteria [4-9]. Therefore, these two formulations could be useful in targeting metronidazole to the colon. Although the use of polymers in drug delivery is not new, but formulators have devised means of circumventing the high cost of developing new excipients and the stringent regulatory requirements by combining existing and approved excipients. Some of these combinations have reportedly shown better performance than the corresponding individual polymer. Various polymer blends have been studied in order to achieve their desired release kinetics (17). The presence of more than one polymer may result in spatial configuration, but it is also possible that a polymer additive may become part of a gel network (18)

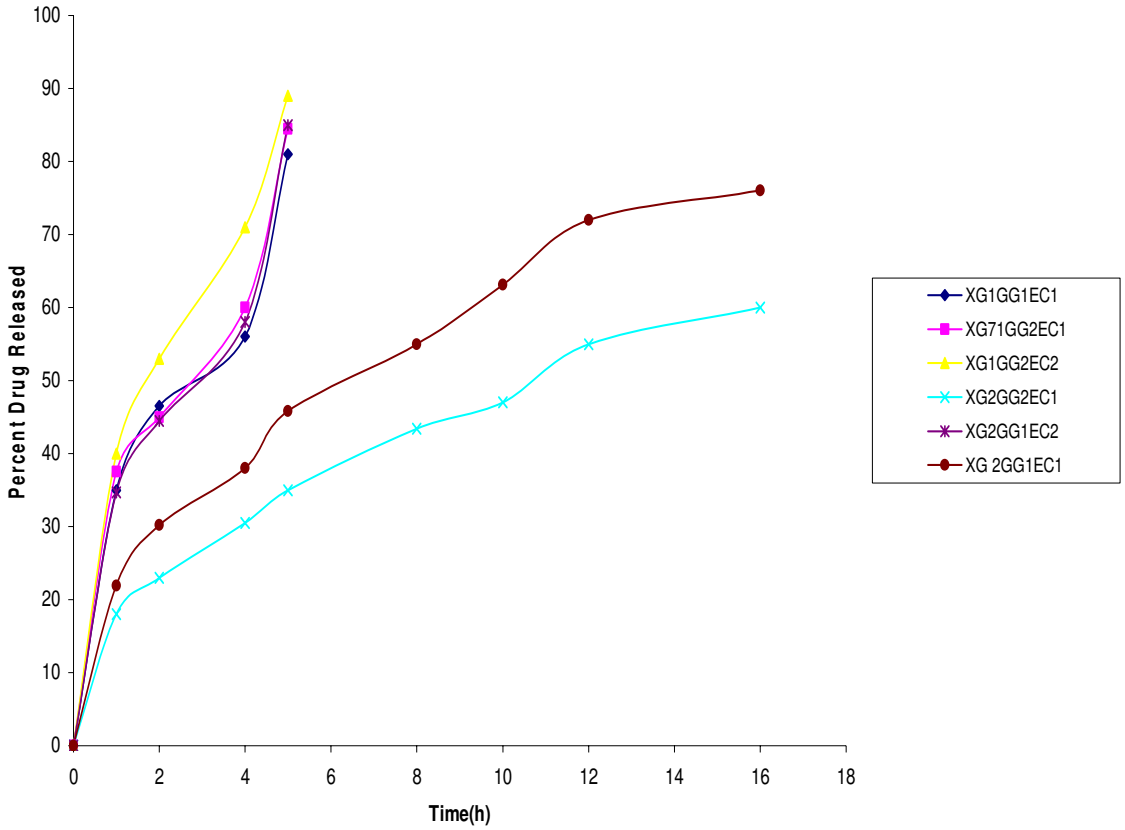

Figure 1: Release profiles of Metronidazole formulations containing various combinations of Xanthan gum (XG), Guar gum (GG) and Ethylcellulose (EC)

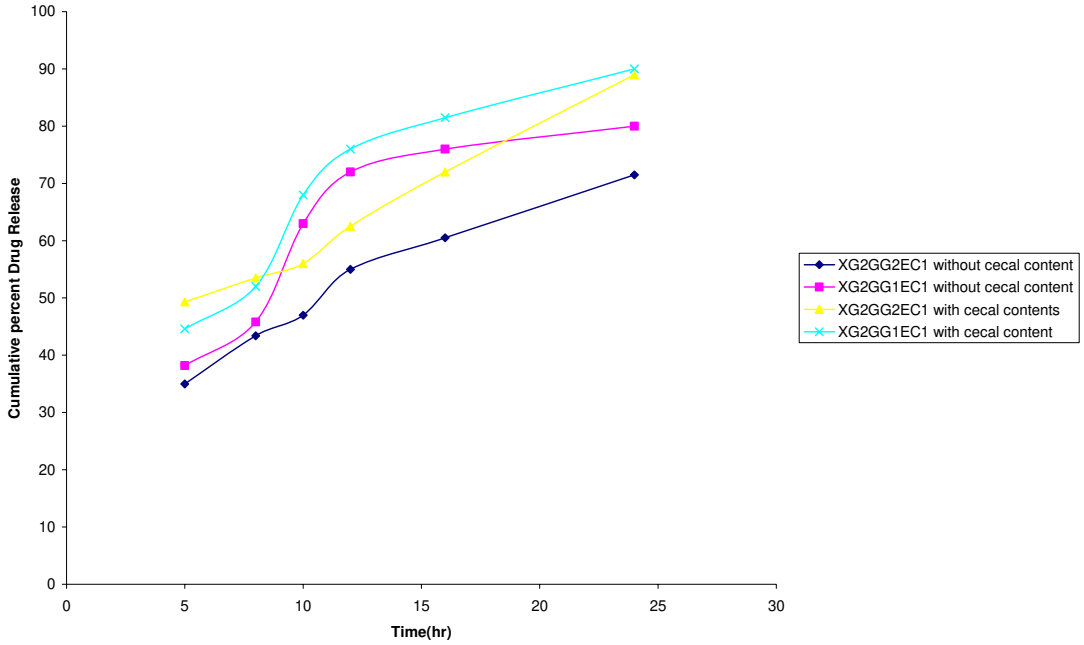

Figure 2: Release profiles of Metronidazole Tablets with and without rat caecal content

Matrix tablets were prepared using blends of Xanthan gum (XG), Guar gum (GG) and ethylcellulose (EC).Metronidazole was used as model drug. The ability of the prepared matrices to retard drug release in the upper gastrointestinal tract (GIT) and to undergo enzymatic hydrolysis by the colonic bacteria was evaluated. For this, drug release studies were carried out in the presence of rat caecal content. Optimum release was observed with metronidazole formulations (XG2GG2EC1, XG2GG1EC1). Formulations containing the three polymers (XG2GG2EC1, XG2GG2EC1) had good drug retarding ability and were susceptible to degradation by colonic bacteria. They followed Higuchi square roots kinetics (r2 =0.9942) via fickian diffusion (n < 0.45) and Korsemeyer model (r2 = 0.9939) via non – fickian diffusion (n > 0.45) respectively.

Authors Contribution

All the authors contributed in the design of the work. Prof Martins did a lot of the editing.

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References

[1]. Walsh JA. Problems in recognition and diagnosis of amoebiasis: estimation of the global magnitude of morbidity and mortality. Rev. Infect. Dis., 1986, 8: 228-238.

[2]. Martindale The Complete Drug Reference, 34th Ed., Sean C. Sweetman (Ed.), The Pharmaceutical Press, 2005.

[3]. Kotla Niranjan, Ashwini Shivapooja, Jagadish Muthyala, Pandya Pinakin Effect of Guar Gum and Xanthan Gum Compression Coating on Release Studies of Metronidazole in Human Fecal Media for Colon Targeted Drug Delivery Systems. Asian J.Pharm.Clin.Res. 2013; 6(2); 315 - 318

[4]. Salve PS. Development and in vitro evaluation colon targeted drug delivery system using natural gums. Asian J. Pharm. Res.2011 ;1 (4): 91-101

[5]. Kajale AD, kamble RS, Giradkar KP, Bakde BV, Channawar MA, Dr. Chandewar AV. Colon Targeted Drug Delivery using Natural PolymerS.Int. J. Pharm. Res.Dev. 2010 ;292: 1-6

[6]. Amit Kumar Panigrahi, Mathrusri.M. Annapurna and K. Himasankar. Polysaccharide Matrix Tablet for Colon Specific Drug Delivery. Int.J.Pharm.Sci. Res.2012 ;3(10) : 3842 - 3846

[7]. Sridhar BK, Srinatha A, Zaman BB , Ragunandan H. Development and Evaluation of Microbial Degradation Dependent Compression Coated Secnidazole Tablets for Colonic

Delivery. Indian J Pharm Sci. 2011; 73(6): 641–648.

[8]. Sinha V R, Mittal B R, Bhutani KK, Kumria Rachna . Colonic drug delivery of 5-fluorouracil: an in vitro evaluation Int J Pharm. 2004 ; 269(1):101-108

[9]. Clement Jackson and Sabinus Ofoefule. Use of Xanthan Gum and Ethylcellulose in Formulation of Metronidazole for Colon Delivery. J. chem. Pharm. Res. 2011 ; 3(2):11-20

[10]. Cooper J and Gunn C. Powder flow and compaction. In: Carter S.J, Tutorial Pharmacy, CBS publishers, New Delhi, 1986; 211 – 233.

[11]. Shah D, Shah Y and Rampradhan M. Development and evaluation of controlled release diltiazem hydrochloride microparticles using cross – linked polyvinyl alcohol. Drug Dev Ind Pharm.1977 ; 23: 567 – 574.

[12]. United States of Pharmacopeia-National Formulary. USP 30 – NF 25. The Unit States Pharmacopeial Convention, Rockville, MD, 2007;Vol. 1, 226.

[13]. Rippe E. Compression of solid and compressed dosage forms. In: Encyclopedia of pharmaceutical technology, Swarhrick, J.Marcel Dekker. Inc., New York, 1990; 149-166.

[14]. Pharmacopoeia of India. Ministry of health and family welfare. Govt. of India, Controller of publications, New Delhi, 1996; vol.II., 736; A-80-83, 147 and 169.

[15]. Leon Lachman, Herhert A, Liberman and Joseph L Karnig. The theory and practice of industrial pharmacy. 3rd ed. Lea and Febigen, Philadelphia, 1986; 430-456.

[16]. Pharmacopoeia of India. Ministry of health and family welfare. Govt. of India, Controller of publications, New Delhi, 2007; vol.II, 1795.

[17]. United States Pharmacopoeial Convention (USP) 1999, USP 24- NF – 19, Rockville, USA

[18]. Sinha VR, Mittal BR, Bhutani KK, Rachna Kumari . Colonic drug Delivery of 5–fluorouracil:an in vitro evaluation. Int J.Pharm. 2004;269:101 -108

[19]. Merchant H A, Shoiab H M , Tazeen J, Yousuf R I. A once daily Tablet formulation and in vitro release evaluation of cepfodoxime usingHydroxypropylmethylcellulose: a technical note: AAPS Pharm. SciTech 2006 ;7 (3) article 78

[20]. Wilmington DE. Polymer blend matrix for oral sustained drug delivery. Pharm .tech. report 016. Hercules Incorporated, Aqualon Division.2002

[21]. Emeje MO. Effect of Molecular size and some Hydrophobic polymers on the sustained release performance of a gel forming polymer:M.Pharm Dissertation, University of Nigeria, Nsukka. 2005.

[22]. Martins EMEJE, Phyllis NWABUNIKE, Yetunde ISIMI, Olobayo KUNLE, Sabinus OFOEFULE. Preparation and evaluation of colon targeted drug delivery systems for albendazole using kneading, extrusion and compaction technology. Acta Pharmaceutica Sinica 2009, 44 (10): 1152-1158]

[23]. Shirwikar A, Annie Shirwaikar , Aravina Kumar G. Herbal Excipients in Novel drug Delivery systems. Indian J.Pharm.Sci. 2008 ;70 (4):415 - 422

[24]. Gohel MC, Amin AF, Patel KV, Panchal MK . Studies in release behaviour of diltiazem HCl from matrix tablets containing (hydroxypropyl) methylcellulose and xanthan gum. Boll Chim farm. 2002 ;141; 21 - 28

[25]. Guide for the care and Use of Laboratory animals. Eight Ed . National Academic Press. Washington D.C.2011