Ternary Blends of Some Hydrophilic and Hydrophobic Polymers in Colon Targeted Delivery of Diethylcarbamazine

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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. Diethylcarbamazine (DEC) was used as the model drug. The ability of the prepared matrices to target drug release at the colon under the influence of colonic bacteria was evaluated using the dissolution medium containing 4% caecal content. Optimum release of drug was observed with formulations XG2GG2EC1 and XG2GG1EC1 with maximum drug release of 75 and 81%, respectively. Significant difference ($P<0.05$) was observed between drug release in dissolution medium with and without rat caecal contents for the batches of DEC tablets. Formulations (XG2GG2EC1 and XG2GG1EC1) followed Korsemeyer models ($r2 = 0.9903$ and $r2 = 0.9955$) respectively via non – fickian diffusion ($n \geq 0.45$).

Keywords: Matrix, guar, xanthan, ethylcellulose, Diethylcarbamazine, colon delivery.

1. 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]

The only effective drug for filariasis is diethylcarbamazine citrate (DEC). This drug

should be delivered to colon for its effective action against microfilariae. The administration of this drug in conventional tablet dosage form provides minimal amount of diethylcarbamazine for local action in the colon. This will result in the relief of filariasis, but with unwanted systemic side effects [26].

Oral administration of conventional dosage forms normally leads to dissolution in stomach fluid followed by absorption from these regions of the gastrointestinal tract[2]. It is a serious drawback in conditions where localized delivery of the drugs in the colon is required or in conditions where a drug needs to be protected from the hostile environment of upper GIT. 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 little or no information on the blends of these polymers in colon targeting.

Literature search shows that, these three polymers

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have never been utilized as blends for colon targeting of diethylcarbamzine. The objective of the present study therefore, was to investigate the development of various diethylcarbamazine colon-specific delivery systems that could be formulated by using ternary blends of ethylcellulose, guar and xanthan gums.

MATERIALS

Diethylcarbamazine, 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 laboratory grade.

METHODS

Experimentals

Preparation of Diethylcarbamazine 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 continued for 10 minutes and the powder mixtures were 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. Drug compacts were stored in airtight specimen bottles and allowed to equilibrate 24 hours before further evaluations.

Table 1. Composition of DEC 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. Percentages were calculated based on total amount of active ingredient (drug).

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

Thickness and hardness [13] as well as friability [14] and weight variation[15] using standard methods were evaluated. The method described by the Indian Pharmacopoeia [16] was used to evaluate uniformity of content

Preparation of rat cecal content medium

The method of Emeje et al [22] was adopted for this

study. Wistar rats weighing 150-200g and maintained on a normal diet (soaked gram) were used. Forty-five minutes before drug release studies, seven rats were killed by spinal traction. The abdomen were opened, the caecal were traced, ligated at both the ends, dissected, and immediately transferred into pH 7.4 buffer previously bubbled with nitrogen. The caecal 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 caecal 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.

Statistical data analysis

The statistical significance was assessed using one-way analysis of variance (ANOVA) with post hoc pair wise comparisons between groups using the Duncan method. For all analyses, $P < 0.05$ was considered significant. Statistical analysis was performed using the computer statistical package SPSS/17.0 (SPSS, Chicago, IL, USA).

In-vitro drug release studies

The ability of matrix tablets of DEC 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°C) in 500 ml 0.1 N HCI 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 Shimadzu UV Spectrophotometer (Shimadzu, Japan) . 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°C) with slight modification. A beaker (capacity 150 mL) containing 100 mL of dissolutionn 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 (5 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 270 nm.

Drug release kinetics

To analyze the mechanism of drug release rate kinetics, the results of *in vitro* release profile were plotted in various kinetic models like zero order, first order, Higuchi model and Korsmeyer – Peppas Equation [19].

RESULTS AND DISCUSSION

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 38 – 41° C. The bulk and tapped densities were found to be in the range of 0.545- 0.571 gm/cc and 0.706 -0.833 gm/cc, respectively. The Hausner ratio was found to be 1.2 to 1.5 indicating moderate flow characters of the powder mixtures (table 2).

Table 2. Evaluation of DEC matrix powder mix

parameters	Formulations					
	XG1GG1EC1	XG1GG2EC1	XG1GG2EC2	XG2GG2EC1	XG2GG1EC2	XG2GG1EC1
Angle of repose (0)	40.91	41.13	40.38	40.6	40.6	38.65
Bulk density (gm/cc)	0.571	0.545	0.545	0.545	0.545	0.545
Tapped density (gm/cc)	0.750	0.732	0.706	0.750	0.750	0.833
Hausner ratio	1.313	1.343	1.295	1.376	1.376	1.529

Table 3. Evaluation of DEC matrix tablets

parameters	Formulations					
	XG1GG1EC1	XG1GG2EC1	XG1GG2EC2	XG2GG2EC1	XG2GG1EC2	XG2GG1EC1
Hardness (kg/cm2)	4.6±0.39	4.45±0.50	4.35±0.47	4.45±0.37	4.55±0.32	4.55±0.60
Weight (mg)	498.2±2.9	497.4±4.45	497.9±3.17	497.8±2.78	497.8±3.33	498.5±3.03
Friability	0.4	0.8	0.8	1.0	0.8	0.8
Drug content (%)	98	98.6	97.5	97	99	98.
Thickness (mm)	4.94±0.04	4.99±0.02	5.00±0.03	4.97±0.08	5.00±0.04	4.96±0.04
Diameter (mm)	12.68±0.02	12.69±0.02	12.69±0.02	12.66±0.03	12.69±0.01	12.64±0.01

Table 4. Some Release parameters of DEC Tablets

parameters	Formulations					
	XG1GG1EC1	XG1GG2EC1	XG1GG2EC2	XG2GG2EC1	XG2GG1EC2	XG2GG1EC1
T50 (h)	0.95	0.79	0.84	9.50	0.96	5.00
T70 (h)	2.60	1.80	2.00	15.60	2.18	11.00
Cmax (%)	90.00	89.00	94.00	70.00	91.00	81.00

Table 5. Release rate constants and release exponents

formulation	Zero-order	First – order	Higuchi	Korsmeyer (n)
XG2GG2EC1	0.9844	0.9858	0.9866	0.9903 (0.46)
XG2GG1EC1	0.9589	0.9955	0.9934	0.9942 (0.45)

The hardness of the tablets for all the formulations was in the range of 4.4 - 4.6 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 or equal to 1 %. Drug content of all the formulations were found to be in the range of 97 to 99% (table-3). All the results are within the prescribed limits[13].

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 were calculated and 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].

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 Cumulative percent drug release values for XG1GG1EC1, XG1GG2EC1, XG1GG2EC2, XG2GG2EC1. XG2GG1EC2 and XG2GG1EC1 were 90%, 89%, 94%, 70%, 91% and 81% 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].

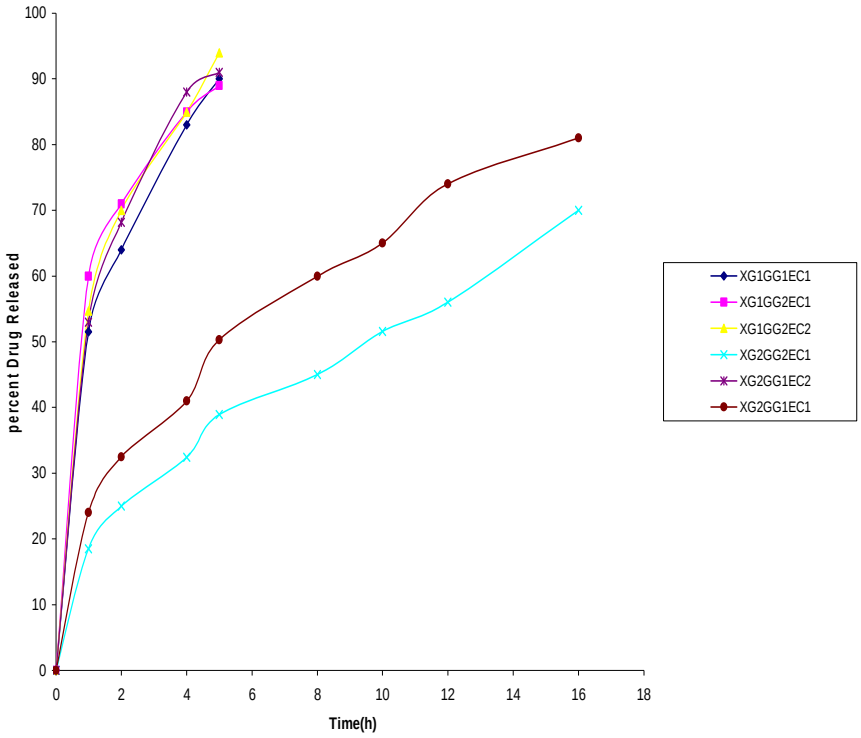

Figure 1: Release profiles of Diethylcarbamazine formulations containing various combinations of Xanthan gum (XG), Guar gum (GG) and Ethylcellulose (EC)

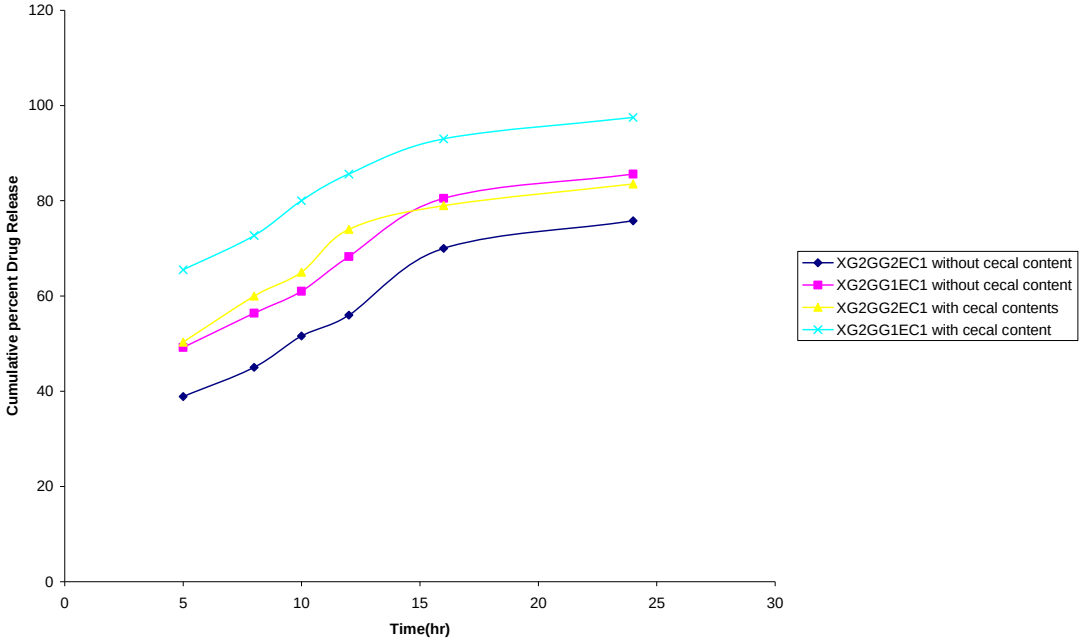

Figure 2: Release profiles of Diethylcarbamzine Tablets with and without rat caecal content

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 75.8% and 83.5% in the absence of rat caecal contents (control) to 85.6 % and 97.8 % (Figure 2) in the presence of rat caecal matter, respectively, indicating that polysaccharide metabolizing enzyme is present in the rat caecal contents. 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 DEC 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]

CONCLUSION

Formulations containing the three polymers (XG2GG2EC1, XG2GG2EC1) had good drug retarding ability and were susceptible to degradation by colonic bacteria. They followed Korsemeyer model ($r2 = 0.9903$) and first order kinetics ($r2 = 0.9955$) respectively via non-fickian diffusion ($n > 0.45$).

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Conflict of Interest

There was no conflict of interest.

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خليط ثلاثي لبعض البوليمرات المحبة للماء وغير المحبة للماء بهدف إيتاء دواء (داي إيثيل كاربامازين) في القولون

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ملخص

تم تحضير أقراص مطرس باستخدام مزيج من صمغ الزانثان وصمغ الجوار والإثيل سيليلوز. أما البوليمرات فقد تم تشكيلها باستخدام ستة نسب مختلفة؛ 1:1:1، 1:2:1، 1:2:2، 2:2:1، 2:1:2 و2:1:1 لإنتاج التوليفات التالية على التوالي؛ XG1GG1EC1)، XG1GG2EC1، XG1GG2EC2، XG2GG2EC1، XG2GG1EC2 و XG2GG1EC1) وقد تم استخدام داي إيثيل كاربامازين كدواء أنموذج.

تم تقييم قدرة المطارس المحضرة لتحرير الدواء المستهدف في القولون تحت تأثير البكتيريا القولونية باستخدام وسط إذابة يحتوي على 4% من المحتويات القولونية. التحرر الأمثل تم ملاحظته بالتوليفات XG2GG2EC1 و XG2GG1EC1 وبنسبة قصوى لتحرر الدواء بلغت 75% و80% على التوالي. تم ملاحظة فرق جوهري ذو أهمية إحصائية ($P<0.05$) بين تحرر الدواء في وسط الإذابة بوجود وبعدم وجود المحتويات القولونية المأخوذة من الجرذ لأقراص الداي إثيل كاربامازين. التوليفات XG2GG2EC1 و XG2GG1EC1 تبعت نماذج كورسماير $r2 = 0.9903$ و$r2 = 0.9955$ على التوالي عبر انتشار غير – فيكي ($n \geq 0.45$).

الكلمات الدالة: أقراص المصفوفة، الغاز، زنتان، إيثيل سيللولوز، ثنائي إيثيل كاربامازين، والتسليم القولون.

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