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Research Article

Design and Evaluation of Oral Based Site Specific Targeting of Oxaliplatin to Colorectal Cancer

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Abstract

Objective: The present study is to achieve colon-specific targeted delivery of oxaliplatin for the treatment of colon cancer and also to assess the use of Guar Gum, Locust Bean Gum, Chitosan alone and also with combination of Hydroxy propyl methyl cellulose (HPMC) in the form of a compression-coating on oxaliplatin core tablet.

Methods: The core tablet of 20 mg of Oxaliplatin was coated with various proportions of Guar Gum (GG), Locust Bean Gum (LBG), Chitosan (CS) and HPMC K-100 as a compression coating material. The effects of these polysaccharides, its level and the coat thickness were evaluated. All the batches were subjected for its potential in colon-specific drug delivery by conducting drug release studies in simulated gastric and intestinal fluids. The amount of oxaliplatin released from the compressed coated tablets at different time intervals was estimated by a UV Spectroscopy method.

Results: From the experimental studies the tablets coated with above mentioned coating materials alone with combination of polysaccharides have showed sustained drug release in the colonic environment. In vitro drug release studies was known to follow super case transport- II.

Conclusion: This study indicated that the use of polysaccharides that are biodegraded by colonic microflora could result in comparatively safer and more effective delivery of drugs to the colon and also a new means to achieve colon-specific drug delivery. This study also revealed that this approach prevents the oxaliplatin drug release in the upper gastrointestinal environment.

Keywords: Oxaliplatin; Guar Gum; Locust Bean Gum; Chitosan; Hydroxy Propyl Methyl Cellulose; Colon Specific Targeting

Introduction

Colorectal cancer is the third most common cancer worldwide. About 1.8 million new cases of colorectal cancer were recorded globally in 2018, accounting for 10 per cent of all new cases of cancer [1]. Colorectal cancer is estimated to be responsible for almost 700,000 cancer deaths and is recorded as the fourth most common cause of death from cancer [1]. Colorectal cancer survival depends on the stage at which it is diagnosed, with later-stage diagnosis having poorer survival. The five-year survival rate is 90% for colorectal cancers diagnosed at an early stage compared with 13% for those diagnosed at a late stage [2-4].

Colon is a site where poorly absorbed drug molecule may have an improved bioavailability. Additionally, the colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs [5]. The oral delivery of drugs to the colon can be a potential site for the systemic absorption of several drugs and has applications in variety of therapeutic areas. Developing an oral colon-specific drug delivery system (OCDDS) has garnered significant attention, owing to the distinct characteristics of the colon, such as neutral pH, longer transit time, reduced digestive enzymatic activity and a greater responsiveness to absorption enhancers [6]. An OCDDS possesses practical implications for the treatment of bowel diseases, such as Crohn's disease, ulcerative colitis and colon cancer, and the systemic delivery of protein and peptide drugs that are labile and poorly absorbed in the gastrointestinal tract [7].

Various approaches for targeting drugs to the colon have been widely investigated, including the pH-sensitive polymer-based system, the time-dependent system, and the pressure-dependent release system [8]. However, the similarity in pH between the small intestine and colon and high variations in gastrointestinal retention time rendered the aforementioned approaches less reliable for colon targeting. In contrast, the colonic microflora-activated system has been considered as an alternative approach, since this strategy exploits the distinctive colonic characteristic of abrupt increase in bacterial population and associated enzyme activities, thus accomplishing greater site specificity of drug release. The microflora population of the colon is normally in the range of 10^{11} - 10^{12} CFU/ml, while that of the intestine is less than 10^{3} - 10^{4} CFU/ml. The use of polysaccharides that are biodegraded by colonic microflora could result in comparatively safer and more effective delivery of drugs to the colon [9,10].

Anti-cancer agents like irinotecan, oxaliplatin, leucovorin, fluorouracil, cetuximab, capecitabine, bevacizumab etc. are used for the treatment of colon cancer. Oxaliplatin is a coordination complex that is used in cancer chemotherapy [3]. These platinum based drugs are usually classified as alkylating agents, although they are not actually alkylating groups. For several decades it is been used as a drug of choice for the treatment of colon cancer. It is usually given intravenously. Intravenous administration produces severe systemic toxic effects[6] like ototoxicity, neuropathy, fatigue, neutropenia, hypokalemia, haematological and neural disorders and cardiac manifestations due to its cytotoxicity [11].

However, an attempt will be made to develop an oral based colonic specific drug delivery system that is expected and provide a useful way of targeting an anti-cancer drug to the colon with the potential of much more effective and less toxic colon cancer treatment.

Materials and Methods

Materials

Guar gum, Chitosan and HPMC K-100 were obtained from Fluka Biochemica, Switzerland. Oxaliplatin was purchased from Spectrochem Pvt. Ltd., India. Microcrystalline cellulose, Magnesium stearate and Sodium Starch Glycolate were obtained from Spectrochem Pvt. Ltd., India. Talc and Sodium Lauryl Sulphate and Sodium hydroxide pellets were received from S.D. Fine chem. Ltd., Mumbai, India. Potassium chloride and Potassium bromide (IR grade) were from Thomas Baker, Mumbai, India and Merck specialties Pvt. Ltd., Germany respectively.

Method

Drug excipients compatibility studies (FT-Infrared spectroscopy)

To find out the chemical interaction between the drug (oxaliplatin) and selected polysaccharides (GG, LBG, CS and HPMC) 10 mg of the sample and 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at 10 kg/cm^2 using a hydraulic press. The pellet was placed in the light path and scanned from 400 cm^{-1} to 4000 cm^{-1} in Shimadzu FT-IR spectrophotometer. The spectra obtained were compared and interpreted for the functional group peaks.

Preparation of core tablets

Core tablets of oxaliplatin were prepared by direct compression method. Microcrystalline cellulose (MCC) was used as diluents, Sodium Starch Glycolate was added to obtain a fast disintegration tablet and a mixture of talc - magnesium stearate (2:1) was used as lubricant. Each core tablet (average weight 60 mg) for *in vitro* drug release studies consisted of oxaliplatin (20 mg), micro crystalline cellulose (29 mg), sodium starch glycolate (5 mg), sodium lauryl sulphate (4 mg), talc (1.5 mg) and magnesium stearate (0.5 mg).

The materials were weighed, mixed and passed through a mesh (250 μm) to ensure complete mixing. The tablets were prepared by compressing the thoroughly mixed materials using 5 mm round, flat and plain punches on a single station tablet machine (Cadmach, India). The thickness of the core tablet was 0.2 mm and their crushing strength was checked. It was about 3 kg/cm^2). The core tablets were tested for hardness, friability, drug content, weight variation and drug release characteristics.

Compression coating of oxaliplatin core tablets

The core tablets of oxaliplatin were compression coated with different coat formulation. The compression coat formulations were prepared using varying ratios of guar gum, chitosan and Locust bean gum and hydroxy propyl methyl cellulose (Table 1). The microcrystalline cellulose was added in the formulation as a direct compression aid and mixture of talc-magnesium stearate (2:1) was used as lubricant. The coating material was compressed at the pressure of 5000 kg using 8 mm round, flat and plain punches. The crushing strength of the tablet was 5 kg/cm^2.

Formulation Code	Coat weight (mg)	Coating composition (mg)						
		GG	LBG	CS	HPMC	MCC	MS	Talc
F1	100	70	-	-	-	25	2	3
F2	140	110	-	-	-	25	2	3
F3	180	150	-	-	-	25	2	3
F4	220	190	-	-	-	25	2	3
F5	100	-	70	-	-	25	2	3
F6	140	-	110	-	-	25	2	3
F7	180	-	150	-	-	25	2	3
F8	220	-	190	-	-	25	2	3
F9	100	-	-	70	-	25	2	3
F10	140	-	-	110	-	25	2	3
F11	180	-	-	150	-	25	2	3
F12	220	-	-	190	-	25	2	3
F13	150	60	-	-	60	25	2	3
F14	150	30	-	-	90	25	2	3
F15	150	90	-	-	30	25	2	3
F16	150	-	60	-	60	25	2	3
F17	150	-	30	-	90	25	2	3
F18	150	-	90	-	30	25	2	3
F19	150	-	-	60	60	25	2	3
F20	150	-	-	30	90	25	2	3
F21	150	-	-	90	30	25	2	3

Table 1: Composition of selected polysaccharides used to coat oxaliplatin core tablets.

Physicochemical evaluation of oxaliplatin compression core and coated tablets

Hardness test and friability test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using the strokes - Monsanto hardness tester. It is expressed in kg/cm^2. In all cases the mean of 10 replicate were determined and the mean and standard deviation values was calculated [12]. The friability of the tablets from each formulation was also tested by using Roche friabilator. It is expressed in percentage (%).

Weight variation test

The procedure described in the I.P. 1996 was employed to determine the weight variation of the tablets. Twenty tablets from each formulation were weighed on an electronic balance and the mean weight was taken. The mean weight was calculated. Each tablet was then weighed separately and the standard deviation in weight was calculated for each formulation [12]. The percent deviation of each tablets weight against the average weight was calculated.

Uniformity of drug content

The prepared oxaliplatin tablets were tested for their drug content. Five tablets of each formulation were weighed and finely powdered. About 0.1 gm equivalent of oxaliplatin was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered [13]. 1 ml of the filtrate was further diluted to 100 ml with pH 6.8 buffer. Absorbance of the resulting solution was measured by U.V visible spectrophotometer at 248.5 nm and the amount of drug in the solution was calculated using the standard curve (r^2 = 0.999).

In vitro drug release studies

The ability of retarding drug release in the physiological environment of stomach and the small intestine with respect to time of compression-coated oxaliplatin core tablets were evaluated under condition mimicking mouth to colon transit [14]. These studies were carried out using USP XXII/XXIII dissolution rate test apparatus (Apparatus 1, 100 rpm, 37°C). 900 ml of 0.1N HCl was used as dissolution medium for 2 h as the average gastric emptying time

(2h) for drug release. Then, the dissolution medium was replaced with pH 7.4 phosphate buffer (900 ml) and tested for 3h as the average small intestine transit time is about 3h. At the end of time periods, the samples from both each of 1 ml were taken separately, suitably diluted and analyzed spectrometrically. The susceptibility of the selected polysaccharides coats to the enzymatic action of colonic bacteria was assessed by continuing the drug release studies in 200 ml of pH 6.8 phosphate buffer containing 4% w/v rat caecal contents until completion of 24h (as usual colonic transit time is 20 - 30h) [15].

The caecal contents were obtained from albino rats after pretreatment for 7 days with selected polysaccharides dispersion which provided the best condition for the *in vitro* evaluation of selected polysaccharides. Five rats were sacrificed by spinal traction thirty minutes before the commencement of drug release studies [16]. Their abdomen were opened, the caecum were isolated, ligated at both ends, dissected and immediately transferred into pH 6.8 PBS which is previously bubbled with CO_2. The caecal bags were opened; their contents were individually weighed, pooled and then suspended in PBS to give a final dilution of 4% w/v. As the caecum is naturally anaerobic, all the operations were carried out under CO_2.

Release kinetics

Data obtained from the *in vitro* release studies of compression coated tablets of capecitabine core tablets were fitted to various kinetic equations such as Zero order, First order, Higuchi model and Korsmeyer-Peppas model using following equations: $Q = Q_0 - K_0t$ (For Zero order model), $\ln Q = \ln Q_0 - K_1t$ (for First order model), $Q = K_2t_{1/2}$ (for Higuchi model), and $Q/Q_0 = K t_n$ (for Korsmeyer-Peppas model). Where, K_0 to K_2 were release rate constants, Q/Q_0 was fraction of drug released at time t, K was a constant and n was diffusion constant that indicates general operating release mechanism. For Fickian (diffusion controlled), $n \leq 0.5$; for non-Fickian (anomalous/ zero order) release, 'n' value is in between 0.5 to 1.0; for zero order release, n = 1.0; for super case transport II, $n > 1.0$ [17].

Stability studies

Stability studies were carried out at different temperatures over a period of 3 months for tablets prepared using coat F1, F6, F10, F13, F18 and F20. The tablets were stored in air tight containers at room temperature and at 40°C/75% RH for a period of three months. The samples were analyzed for their drug content [18].

Results and Discussion

The intention of the present work was to formulate different composition of polysaccharides coated of oxaliplatin core tablets by direct compression method to facilitate the maximum drug delivery at the required site to get the therapeutic gain. Twenty one formulations were using different concentration of GG, LBG, CS alone and combination with HPMC and were evaluated to confirm the colon specificity. The quickly disintegrating oxaliplatin core tablets were formulated by direct compression method using super disintegrant sodium starch glycolate and disintegrate within 54 sec which was evaluated in USP disintegration tester. The physicochemical properties of oxaliplatin core and all the batches of compression coated tablets were found to be good and shown within the Pharmacopeial limit and summarized in table 2 and 3. The weight of the compression coated oxaliplatin core tablets weighing between 160 mg - 280 mg were found confined within acceptable limit and the drug content was found in good uniformity among different batches of the tablets.

Hardness (Kg/cm^2) a	Friability (%) b	Weight variation (%) c	Drug content (%) d	Disintegration (sec) e
2.41 ± 0.021	0.201 ± 0.012	1.016 ± 0.025	98.1 ± 0.011	54
a (n = 5 ± S.D)	b(n = 20 ± S.D)	a (n = 20 ± S.D)	d (n = 3 ± S.D)	e (n = 3 ± S.D)

Table 2: Physicochemical evaluation of oxaliplatin core tablets.

The interaction study of oxaliplatin with selected polysaccharides was evaluated using FTIR spectroscopy. The characteristic peaks of oxaliplatin were found at almost the same wave numbers as those situated with drug alone and there was no new peak or elimination of any of the existing peaks was noted. This clearly confirmed that the compatibility of oxaliplatin with selected polysaccharides.

The main reason for selecting these polysaccharides were its biodegradation in the colon by colonic bacteria and high molecular weight HPMC increases the mechanical strength of the table wall around the oxaliplatin core tablet during its transportation in the gastrointestinal tract. The core composition was kept fixed; the effect of variation in compression coated polymer with various concentrations on drug release was evaluated. The coat weight was optimized by determining the *in vitro* drug release studies for the formulations having different coat weights (100 - 220 mg). The formulations F9 (100 mg) released maximum amount of oxaliplatin in the physiological environment of 0.1N HCl (stomach) and the formulations F5 (100 mg) released its drug content in phosphate buffer 7.4 pH (small intestine). So, formulations F5 and F9 are not able to protect the oxaliplatin core tablet to the colonic region as it has not that much coating integrity. This might be due to insufficient of coating composition on oxaliplatin core tablets.

Formulation code	Hardness (Kg/cm^2) a	Friability (%) b	Weight variation (%) c	Drug content (%) d
F1	4.76 ± 0.12	0.46 ± 0.026	0.37 ± 0.011	98.1 ± 0.011
F2	4.54 ± 0.31	0.58 ± 0.054	0.79 ± 0.021	98.16 ± 2.22
F3	5.01 ± 0.14	0.43 ± 0.022	0.65 ± 0.032	99.12 ± 2.15
F4	4.96 ± 0.21	0.28 ± 0.021	0.68 ± 0.025	97.61 ± 1.22
F5	4.79 ± 0.11	0.38 ± 0.031	0.73 ± 0.012	98.12 ± 1.52
F6	4.66 ± 0.15	0.21 ± 0.054	0.94 ± 0.054	98.29 ± 1.56
F7	5.02 ± 0.25	0.53 ± 0.052	0.87 ± 0.065	98.72 ± 1.21
F8	4.72 ± 0.33	0.21 ± 0.021	0.55 ± 0.022	99.15 ± 1.54
F9	4.76 ± 0.35	0.53 ± 0.012	0.72 ± 0.014	97.86 ± 1.26
F10	4.89 ± 0.32	0.37 ± 0.045	0.37 ± 0.032	98.76 ± 2.24
F11	4.77 ± 0.12	0.54 ± 0.044	0.68 ± 0.065	99.15 ± 2.25
F12	4.86 ± 0.25	0.39 ± 0.033	0.46 ± 0.025	98.17 ± 2.64
F13	4.88 ± 0.15	0.29 ± 0.022	0.65 ± 0.018	96.98 ± 2.64
F14	4.69 ± 0.32	0.19 ± 0.025	0.73 ± 0.014	97.84 ± 3.12
F15	4.92 ± 0.52	0.47 ± 0.052	0.94 ± 0.041	98.17 ± 2.456
F16	5.05 ± 0.24	0.39 ± 0.035	0.56 ± 0.055	98.14 ± 2.16
F17	4.96 ± 0.15	0.60 ± 0.054	0.55 ± 0.048	98.63 ± 2.15
F18	4.29 ± 0.25	0.57 ± 0.025	0.59 ± 0.067	97.19 ± 1.21
F19	4.55 ± 0.36	0.24 ± 0.035	0.68 ± 0.022	98.76 ± 1.15
F20	5.12 ± 0.62	0.33 ± 0.045	0.61 ± 0.032	99.01 ± 1.21
F21	4.39 ± 0.18	0.58 ± 0.064	0.45 ± 0.025	96.79 ± 1.36
	a (n = 5 ± S.D)	b (n = 20 ± S.D)	c (n = 20 ± S.D)	d (n = 3 ± S.D)

Table 3: Physicochemical evaluation of compression coated oxaliplatin core tablets.

Figure 1: (a) Oxaliplatin core tablets (b) Compression coated Oxaliplatin core tablets using GG.

Figure 2: IR spectrum of Oxaliplatin.

Functional group	IR band of oxaliplatin, cm^{-1}	IR band of physical mixture of selected polysaccharides, cm^{-1}
-NH	3090.07	3093.7
-CH	2929.97	2928.04
C=O	1705.13	1701.27
C-N	1224.84	1224.84
-C-O	1379.15	1379.15

Table 4: IR interpretation of oxaliplatin and physical mixture of drug and polymer.

Figure 3: IR spectrum of physical mixture of oxaliplatin, GG, LBG, CS and HPMC.

Increase in concentration of LBG, GG and CS and its coating weight lead to increase in release lag time and decrease in release rate. Figure 6-8 showed the outcome results of the increase in the quantity of GG, LBG and CS (polysaccharides) alone and with HPMC combination in the coated tablets. The increase in the concentration of polysaccharides coat made the drug release slower. At the end of 26th h the formulations F2, F6, F12, F17, F20 and F23 released maximum amount of drug at a time interval of 8 - 12h and the tablet coat has completely disintegrated, hence selected as best formulations. Whereas the other formulations F3, F4, F7, F8, F9 released the drug but the compression coat was remained contact till end (Figure 4 and 5).

Figure 4: Picture of guar gum compression coated tablet after dissolution studies after 2h, 5h, 10h and 26h.

Figure 5: Picture of LBG (a) and CS (b) compression coated tablet after dissolution studies after 26h (220 mg of coat weight).

Figure 6: Collective % oxaliplatin release profile of from different composition of coating material of GG (F1-F4) and combination with HPMC (F13-F15).

Figure 7: Collective % oxaliplatin release profile of from different composition of coating material of LBG (F5-F8) and combination with HPMC (F16-F18).

Figure 8: Collective % oxaliplatin release profile of from different composition of coating material of CS (F9-F12) and combination with HPMC (F19-F21).

Compression coated oxaliplatin core tablet was able to retard the drug release in upper GIT which is highly helpful to reduce side effects in the GIT and further the controlled release pattern in the

colon 80 - 90% at 26th h. Hence such a design may be used for colon targeted delivery of oxaliplatin for the treatment of cancer. The results of the release studies be evidence for that the compression coating with selected polysaccharide was possible to protect the drug release in the stomach and small intestine, but also provide control release the drug in the colon.

To assess the capability and integrity of coat on drug release studies were continued without addition of rat caecal content and the collective % drug release was found to be 20 - 39% (Figure 8-10). The results revealed that the drug release was occurred by the degradation of the coat material by the enzymes in the caecal

Formulation Code	Zero Order		First Order		Higuchi		Korsmeyer – Peppas	
	r^2	n	r^2	n	r^2	n	r^2	N
F1	0.966	4.28	0.863	0.09	0.806	21.69	0.904	1.73
F6	0.962	4.10	0.873	0.09	0.789	20.11	0.899	1.70
F10	0.968	4.31	0.834	0.09	0.821	21.49	0.899	1.72
F14	0.975	4.13	0.838	0.09	0.817	20.47	0.902	1.70
F17	0.962	4.06	0.849	0.09	0.812	19.89	0.902	1.69
F20	0.962	4.06	0.849	0.09	0.812	19.89	0.901	1.67

Table 5: Regression co-efficient (r^2) values and diffusion exponent (n) of Korsmeyer-Peppas model for compressed coated oxaliplatin core tablets.

contents and also colonic media can dramatically promote drug release, the potential for colon-specific drug delivery was confirmed.

Drug release data were fitted with various kinetics models and evaluated the drug release mechanism. It was followed by zero order kinetics and diffusion controlled. Further the value of 'n' from Korsemeyer-Peppas equation revealed the release was followed supercase transport-II. The results were given in the table 5.

Figure 9: Collective % oxaliplatin release profile of from different composition of coating material of GG (F1-F4) and combination with HPMC (F13-F15).

The data of stability studies after storage of three months revealed that there was no major change in physical parameters and percentage drug content during the study period (Table 6). This

Figure 10: Collective % oxaliplatin release profile of from different composition of coating material of LBG (F5-F8) and combination with HPMC (F16-F18).

Figure 11: Collective % oxaliplatin release profile of from different composition of coating material of CS (F9-F12) and combination with HPMC (F19-F21).

Formulation	Time duration in months	Hardness kg/cm^2	Friability (%)	Drug content
F1	1 - 3	4.66-4.8 ± 0.32	0.49-0.52 ± 0.14	98.54-99.16 ± 2.36
F6	1 - 3	4.67-4.98 ± 0.45	0.47-0.59 ± 0.64	97.25-99.56 ± 2.1
F10	1 - 3	4.69-4.76 ± 0.16	0.54-0.72 ± 0.22	95.54-98.53 ± 2.58
F14	1 - 3	4.95-5.16 ± 0.44	0.24-0.62 ± 0.57	95.18-99.19 ± 3.12
F17	1 - 3	4.86-5.16 ± 0.42	0.46-0.52 ± 0.25	96.35-99.12 ± 3.22
F20	1 - 3	4.69-5.21 ± 0.36	0.57-0.64 ± 0.85	95.16-98.26 ± 3.11

Table 6: Stability study results of selected formulations stored at 40°C ± 2°C/75% ± 5% RH.

indicated that formulated tablet exhibited good physical stability for 3 months.

Conclusion

This study demonstrated and assessed the use of guar gum, locust bean gum, chitosan alone and with combination with hydroxy propyl methyl cellulose in the coat of a compression-coated tablet to achieve colon-specific drug delivery. Oxaliplatin core tablets were prepared by direct compression and the effects of the coat thickness were evaluated. The product was tested for its potential in colon-specific drug delivery by conducting release studies in simulated gastric, intestinal fluids and also under colonic conditions. The planned site-specific delivery of oxaliplatin from compression coated system may trim down the side effects and also shield the release of the drug from the upper part of the GI tract when given in conventional dosage forms. The experimental results illustrated that the selected polysaccharides (guar gum, locust bean gum, chitosan alone and with combination with hydroxy propyl methyl cellulose) have the potential to be used as a carrier in the form of compression coating for an effective colon site specific targeted delivery system to get desired therapeutic action

Conflicts of Interest

The authors report no conflict of interests.

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