Supplementary

Carbohydrate Polymer-Based Targeted Pharmaceutical Formulations for Colorectal Cancer: Systematic Review of the Literature

Samia Farhaj [1], Theodora L. Agbotui [1], Jorabar Singh Nirwan [1], Qaisar Mahmood [2,3], Abid Mehmood Yousaf [4], Talib Hussain [5], Yasser Shahzad [4], Nemat Khan [6], Barbara R. Conway [1] and Muhammad Usman Ghori [1,*]

[1] Department of Pharmacy, School of Applied Sciences, University of Huddersfield, Huddersfield HD1 3DH, UK
[2] College of Pharmaceutical Sciences, Zhejiang University, Hangzhou 310058, China
[3] Department of Pharmaceutical Sciences, Biomanufacturing Research Institute & Technology Enterprise, North Carolina Central University, Durham, NC 27707, USA
[4] Department of Pharmacy, COMSATS University Islamabad, Lahore Campus, Lahore 45550, Pakistan
[5] Secretary District Quality Control Board, Rawalpindi 46000, Pakistan
[6] School of Biomedical Sciences, Faculty of Medicine, The University of Queensland, Brisbane, QLD 4702, Australia
* Correspondence: m.ghori@hud.ac.uk; Tel.: +44-(0)-1484-256950

Table S1. Study characteristics of carbohydrate-based polymers used to provide targeted delivery.

Study ID	Drug	Polymer (s)	Study characteristics	References
(Wang et al., 2007)	5-FU	Pectin	5-FU-1-acetic acid with pectin conjugate was synthesised and evaluated for colon targeting drug delivery. After *in vivo* studies, the pectin conjugation efficiently delivered drug to the colon and caecum of rats.	[55]
(Jain et al., 2007)	5-FU	Pectin and Eudragit S-100	Calcium pectinate beads were formulated containing 5-FU with enteric coating of Eudragit S-100 to provide colon specific delivery system. After *in vitro* and *in vivo* studies the drug was effectively delivered to the colonic region.	[56]
(Paharia et al., 2007)	5-FU	Pectin and Eudragit	Eudragit-coated pectin microspheres for colon targeting of 5-FU were developed. The release of drug from Eudragit coated microspheres was pH dependant. In alkaline medium the drug release was quicker compared to gastric medium (*in vitro* and *in vivo*)	[57]
(Wei et al., 2008)	5-FU	Pectin /ethyl cellulose	*In vitro* and *in vivo* characteristics of pectin/ethylcellulose film coated drug containing pellets were evaluated. The coated pellets displayed satisfactory drug release profile in colonic fluid (*In vitro*) along with delayed T_{max},	[58]

			decreased C_{max} and prolonged mean resistance time (*in vivo* studies).	
(Elyagoby et al., 2013)	5-FU	Pectin and Ethylcellulose	*In situ intracapsular* coating of ethylcellulose on zinc-pectinate pellets was conducted to provide targeted drug delivery on colon. After *in vitro* and *in vivo* studies the hydrophobic layer of ethylcellulose delayed the release of drug in the upper GI tract and effectively delivered drug and pectin to the colonic region for the treatment of colon cancer.	[59]
(Subudhi et al., 2015)	5-FU	Pectin and Eudragit S100	Eudragit S100 coated citrus pectin nanoparticles containing drug were fabricated. The multifaceted strategy of pectin indicated receptor mediated uptake of nanoparticles over cancer cells with targeted drug release in the colonic region.	[60]
(Andishmand et al. ,2017)	Resveratrol	Pectin and Chitosan	Nanoparticles of pectin-zinc-chitosan with polyethylene glycol were formulated. The formulated NPs released minimal drug amount in simulated gastric fluid. Whereas ∼49% of the drug was released in simulated colonic environment	[61]

(Zhu et al., 2019)	Doxorubicin hydrochloride	Pectin, Chitosan, and Starch	Doxorubicin-loaded PS granules were coated with pectin or pectin/chitosan. The coated beads released negligible amount of drug in GIT thus indicating that greater drug could be delivered to the colon.	[62]
(Ansari et al., 2019)	Pterostilbene:	Pectin and Eudragit S-100	Colon targeted beads loaded with drug and coated with Eudragit S-100 were formulated. *In vitro* studies displayed larger amount of drug in the colonic tissue in comparison to stomach and small intestine region.	[63]
(Sabra et al., 2019)	Curcumin	Citrus pectin and Chitosan	Drug-loaded modified pectinate chitosan nanoparticulate carrier system was formulated. Quantitative and qualitative analysis displayed enhanced cellular uptake of drug from nanoparticulate carrier system.	[64]
(Sabra et al., 2019)	Curcumin and cetuximab	Citrus pectin and Chitosan	Cetuximab-conjugated modified citrus pectin-chitosan nanoparticles for targeted delivery of curcumin were formulated. The nanoparticles displayed appropriate drug release along with significant reduction of cancer cells growth.	[65]

(Tığlı Aydın & Pulat, 2012)	5-FU	Chitosan	Drug encapsulated chitosan-based nanoparticles were developed. The optimised nanoparticles displayed narrow size distribution with controlled and sustained drug release profile required for the treatment of colorectal cancer	[66]
(Dilip, 2016)	Capecitabine	Chitosan	Chitosan based microspheres containing drug were formulated. The release profile demonstrated initial burst release of drug in GI tract. Therefore, microencapsulation of microspheres is required.	[67]
(Liu et al., 2018)	5-FU	Galactosylated chitosan	Drug loaded amino-functionalized mesoporous silica nanoparticles were developed. The nanoparticles displayed higher cytotoxicity along with sustained release effect by recognition of galectin-receptor on the cancer cells	[68]
(Woraphatphadung et al., 2018)	Curcumin	Chitosan	pH-sensitive polymeric nanoparticles carrier micelles were developed. The N-naphthyl-N,O-succinyl chitosan based micelles exhibited higher anticancer effect against colorectal cancer cells.	[69]
(Dodov et al., 2009)	5-FU	chitosan–Ca–alginate	Lectin-conjugated chitosan-Ca-alginate microparticles containing 5-FU after conjugation with wheat germ agglutinin were formulated. The microparticles exhibited controlled drug release manner along with higher drug concentration at the local site.	[70]

(Sinha et al., 2018)	Capecitabine	Chitosan succinate and alginate	Chitosan succinate-sodium alginate macromolecular complex beads containing drug were formulated. The beads successfully release most of the drug in the colon.	[71]
(Tummala et al., 2015)	5-FU	Chitosan and Eudragit L 100	Drug encapsulated chitosan based enteric coated nanoparticles were formulated. The optimised drug polymer ratio displayed higher entrapment efficiency along with targeted and prolonged drug release in the intestinal medium (*in vitro*).	[72]
(Jain & Jain, 2016)	5-FU	Chitosan and Hyaluronic acid	Bioavailability of orally administered anticancer drug was evaluated after enteric coating. The release of drug was protected in both gastric and intestinal mediums but provided high local drug concentration on the targeted site(colon).	[73]
(Patel, 2017)	Meloxicam	Chitosan and Eudragit 100	Chitosan-based drug loaded enteric coated tablets of microspheres were developed. The coated tablets displayed no drug release in upper GI tract. The optimised batch released drug in the region of colon.	[74]
(Krishnaiah et al., 2002)	5-FU	Guar gum (GG)	Guar gum coated tablets were formulated. The compressed tablets with 80% polymer coat released only 2.85% drug in stomach and intestinal mediums while 41% was released in the colonic medium	[75]

(Krishnaiah el al., 2003)	5-FU	Guar-gum	*In vivo* pharmacokinetics of guar gum-based tablets were evaluated against immediate release tablets. The coated tablets displayed targeted drug release in the colon compared to immediate release tablets	[76]
(Chaurasia et al., 2006)	Methotrexate	Guar gum	Cross-linked polymer-based microspheres were formulated. After *in vitro* and *in vivo* studies the formulation displayed adequate potential for achieving specific colonic drug delivery.	[77]
(Singhal et al., 2011)	Quercetin	Guar gum	Polymer based matrix tablets were formulated. *In vitro* studies revealed no drug release in the upper GI tract but targeted drug release in the colonic region	[78]
(Vats & Pathak, 2012)	Piroxicam	Guar gum, Eudragit S100	An oral targeted tablet of piroxicam microspheres were formulated. The coated tablets released 97.1% drug in simulated colonic fluid.	[79]
(Singh et al., 2015)	5-FU	Guar-gum and Xanthan gum	Oral delivery of active moiety was improved by probiotic and prebiotic approach. The coated drug remained protected in GI fluid but released maximum amount of drug in the colonic region	[80]
(Kumar et al., 2017)	5-FU	Guar-gum	Mesoporous based silica nanoparticles were formulated coated with guar gum (GG-MSN). No undesired leakage of drug release was observed in the GI tract. The drug release from GG-MSN is triggered by the colonic region and	[81]

			subsequently drug release occurred in the vicinity of the colon cancer cells	
(Kamal et al., 2017)	5-FU	Guar gum	Cross linked polymer-based microspheres were formulated. The prepared formulation could control the release of drug over 24 hours with targeted delivery in the colon.	[82]
(Zhang et al., 2017)	5-FU	Sodium alginate	GO-ALG/5-FU drug delivery system was formulated. After *in vitro* and *in vivo* studies the system displayed targeted drug delivery along with minimal toxicity.	[83]
(Rahman et al., 2006)	5-FU	Alginate and Eudragit S100	Colonic specific microspheres were formulated. The formulation with 1:7 drug polymer ratio displayed sustained release for up to 20 hours in the progression medium mimicking the conditions of GIT. Moreover, no change in physicochemical nor release profile was observed after 6 months of stability studies.	[84]
(Rahman et al., 2008)	5-FU	Alginate, Eudragit	The *in vivo* evaluation of enteric coated sodium alginate microspheres was performed. After pharmacokinetic studies, no drug release was observed in GI tract and intestinal region. While significantly higher level of drug concentration was obtained in colonic tissues.	[85]

(Ma & Coombes, 2014)	Indomethacin	Eudragit RS30D NPs, Alginate	Drug loaded enteric coated pellets were encapsulated in alginate as a carrier. Significantly higher fraction of drug load of around 60% was released in simulated colonic fluid.	[86]
(Agarwal et al., 2015)	5-FU	Calcium alginate - carboxymethyl cellulose	Calcium alginate carboxymethyl cellulose beads were formulated. The formulated beads successfully delivered the drug towards the colonic region.	[87]
(Sookkasem at al., 2015)	Curcumin	Alginate and Eudragit® S-100	Alginate beads coated with Eudragit® S-100 were formulated. The optimised formulation released more than half of the drug in the simulated colonic fluid.	[88]
(Asnani & Kokare, 2018)	5-FU	Portulaca-alginate	Crosslinked hydrogel-based beads were formulated. The microspheres displayed sustained release effect along with higher concentration at the colonic region.	[89]
(Feng et al., 2019)	Salmon calcitonin	Sodium alginate and pectin	Polysaccharide based multi-unit nanofiber mat was formulated to provide a sustain release effect in the colon. *In vitro* release studies demonstrated greater amount of drug release in SCF in a sustained release manner.	[90]
Sun et al.,	5-FU	Alginate, Chitosan, and kappa-carrageenan	Dual-layered pH-sensitive microbeads were formulated. The microbeads displayed higher percentage of drug release in SCF in comparison to simulated SGF.	[91]

(Jain & Jain, 2008)	5-FU	Hyaluronic acid (HA) coupled chitosan	Hyaluronic acid coupled with chitosan-based nanoparticles were formulated. The coupled nanoparticles displayed higher uptake of cancer cells along with higher toxicity.	[92]
(Jain el al., 2010)	Oxaliplatin	Hyaluronic acid–coupled chitosan Eudragit S100	Ligand-appended polysaccharide-based pellets were developed. After *in vivo* studies, the pellets delivered higher concentration of drug in the colonic region of mice.	[93]
(Kotla et al, 2019)	Curcumin	Hyaluronan	Polymeric nano particles containing model drug were formulated. The nanoparticles displayed higher drug release towards the target site of colon.	[94]
(Rai et al, 2016)	5-FU	Dextran, Eudragit S-100 L/S 100	Enteric coated dextran microspheres for colon targeting of drug were formulated. The microspheres displayed no drug release in the GI tract while slower and continuous drug release was observed in the colonic region.	[95]
(Raza et al., 2018)	5-FU	Chondroitin sulphate	Chondroitin sulphate–polyvinyl alcohol cross-linked microcapsules were prepared. The optimised formulation displayed maximum drug release in the colonic site.	[96]

Table S2. Assessment of risk of bias for each study included in the systematic review.

	Risk of Biasness parameters						
Study ID	**Research rationale**	**Description of methods**	**Characterisation and testing**	**Description of results**	**Discussion**	**Overall conclusions**	**References**
(Wang et al., 2007)	+	+	+	+	?	+	[55]
(Jain et al., 2007)	+	+	+	+	?	+	[56]
(Paharia et al., 2007)	+	+	+	+	+	+	[57]
(Wei et al., 2008)	+	+	+	+	?	+	[58]
(Elyagoby et al., 2013)	+	+	+	+	?	+	[59]
(Subudhi et al., 2015)	+	+	+	+	+	+	[60]
(Andishmand et al., 2017)	+	+	+	+	+	+	[61]
(Zhu et al., 2019)	+	+	+	+	+	+	[62]
(Ansari et al., 2019)	+	+	+	+	?	+	[63]
(Sabra et al., 2019)	+	+	+	+	?	+	[64]
(Sabra et al., 2019)	+	+	+	+	?	+	[65]
(Tığlı Aydın & Pulat, 2012)	+	+	+	+	+	+	[66]
(Dilip, 2016)	+	+	+	+	?	+	[67]
(Tummala et al., 2015)	+	+	+	+	+	+	[72]

(Jain & Jain, 2016)	+	+	+	+	+	+	[73]
(Liu et al., 2018)	+	+	+	+	+	+	[68]
(Woraphatphadung et al., 2018)	+	+	+	+	+	+	[69]
(Dodov et al., 2009)	+	+	+	+	+	+	[70]
(Patel, 2017)	+	+	+	+	+	+	[74]
Sinha et al., 2018	+	+	+	+	?	+	[71]
(Krishnaiah et al., 2002)	+	?	+	+	+	+	[75]
(Krishnaiah el al., 2003)	+	+	+	+	+	+	[76]
(Chaurasia et al., 2006)	+	+	+	+	?	+	[77]
(Singhal et al., 2011)	+	+	+	?	?	+	[78]
(Vats & Pathak, 2012)	+	+	+	+	+	+	[79]
(Singh et al., 2015)	+	+	+	+	?	+	[80]
(Kumar et al., 2017)	+	?	+	+	?	+	[81]
(Kamal et al., 2017)	+	?	+	+	+	+	[82]
(Zhang et al., 2017)	+	?	+	+	+	+	[83]
(Rahman et al., 2006)	+	+	+	?	?	+	[84]
(Rahman et al., 2008)	+	?	+	+	+	+	[85]
(Ma & Coombes, 2014)	+	+	?	+	+	+	[86]
(Agarwal et al., 2015)	+	+	+	+	+	+	[87]
(Sookkasem et al., 2015)	+	+	+	+	?	+	[88]
(Asnani & Kokare, 2018)	+	+	+	+	+	+	[89]
(Feng at al., 2019)	+	+	+	+	?	+	[90]

(Sun et al., 2019)	+	+	+	+	?	+	[91]
(Jain & Jain, 2008)	+	+	+	+	+	+	[92]
(Jain el al., 2010)	+	+	+	+	+	+	[93]
(Kotla et al, 2019)	+	+	+	+	?	+	[94]
(Rai et al, 2016)	+	+	+	+	+	+	[95]
(Raza et al., 2018)	+	+	+	+	+	+	[96]