COLON-SPECIFIC DRUG DELIVERY-AN OVERVIEW

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In recent years, targeting of drug to the colon is used for treating the colon disorders such as irritable bowel syndrome, ulcerative colitis, Crohn's disease, infectious diseases and colon cancer. Most of the conventional drug delivery systems for treating the colon disorders are failing as the drug do not reach the site of action in appropriate concentration. So site specific delivery of drugs to colon is very much desirable for an effective and safe therapy of colon. This article gives an overview on anatomy and physiology of the colon, factors affecting colonic drug delivery, delivery of peptides and proteins and approaches utilised for colon specific delivery of drugs.

Introduction

Targeting of proteins and peptides to colon for systemic absorption has been attracting much interest due to unprecidented rapid development of biotechnology and genetic engineering resulting in the availability of peptides and protein drugs at reasonable cost. Besides peptides and protein drugs, the colon is also a good site for the absorption of those drugs, that are not stable in the acidic environment of the stomach that causes gastric irritation or those degraded by small intestinal enzymes.

A summarised information on anatomical and physiological characteristics of small intestine and colon are given in the table below.

Region of gastrointestinal tract		Characteristic length (cm)
Entire gastrointestinal tract		500-700
Small intestine	Duodenum	20-30
	Jejunum	150-250
	Ileum	200-350
Large intestine	Cecum	6-7
	Ascending colon	20
	Transverse colon	45
	Descending colon	30
	Sigmoidal colon	40
	Rectum	12
	Anal canal	3
		Internal diameter
Small intestine		3-4
Large intestine		6
		pH
Stomach	Fasted	1.5-3
	Fed	2-5
Small intestine	Duodenum (Fasted)	6.1
	Duodenum (Fed)	5.4
	Ileum	7-8
Large intestine	Cecum and colon	5.5-7
	Rectum	7

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Factors affecting colonic drug delivery

*i) Transit of materials into and through the colon:*Gastric emptying of dosage forms is highly variable and depends primarily on whether the subject is fed or fasted and on the property of dosage forms such as size and density. Compared to other regions of the GI-tract, movement of material through the colon is slow and influenced by a number of factors such as diet, in particular dietary fiber contents, motility, stress, diseases and drugs (1). Total colon transit time is significantly shorter in male than in female(2). However some studies have shown no difference between male and female transit time(3,4). In healthy young and adult males, dosage forms such as capsules and tablets pass through the colon in appoximate 20-30 hours, although a transit time of few hours to more than 2 days can occur(5). Colonic transit is independent of size and density of the dosage forms and it does not discriminate between solid and small volume of liquids(6). In patients with quiescent inflammatory bowel disease, colonic residence of pharmaceutical dosage forms tends to be same as that in heathy subjects(7). The gastrointestinal transit of a radiolabelled non disintegrating osmotic tablet formulation was measured in 6 subjects using gamma scintigraphy. The tablet was emptied from the stomach in a mean time of 0.8 hours. The mean transit time through the small intestine was 3 hours. Colonic transit was highly variable with median transit time of 20.9 hours(8). The results from these studies suggest that smaller units travel through the colon more slowly than larger ones. Hence additional retension of a dosage form within the colon could perhaps be achieved by the use of controlled release dosage forms.

*ii)Colonic bacteria:*The slow movement of material through the colon allows a large microbial population to thrive there. The microbial flora of the colon are predominantly anaerobic and carry out a variety of metabolic reactions like hydrolysis, reduction, decorboxylation etc. These metabolic actions are utilised as a trigger to release the drug specifically in the colon. The colonic bacteria may affect the absorption of drug by their metabolic actions.

*iii) Effect of diet on colonic transit:*The principal dietary component which can affect colonic motility is dietary fiber. It is generally considered that dietary supplementation increases fecal weight, partly by retension of water and partly by increasing bacterial mass and reduces colonic transit time. It was suggested that the fiber may exert a normalisation effect on colon transit, increases it in individuals with slow transit(9). Ingestion of food appeared to be followed by an acceleration of tablet movement through the ileocecal junction into the colon, although the phenomenon was non influenced by types of the meals taken.

iv) Effect of disease on colonic transit: Diseases affecting colonic transit have important implications for drug delivery; diarrhea will result in an increasing and constipation in a decreasing, colonic motility. Poorly absorbed substances retain excessive fluid within the intestinal fluid and this is the mechanism by which substances such as magnesium salts, sorbitol, and polyethylene glycol can cause diarrhea(10). In some patients, inflammatory bowel syndrome is associated with diarrhea and in others with constipation.

PEPTIDES AND PROTEINS

A more elusive goal is to use the colon as a site for the oral absorption of therapeutic peptides and proteins. Al-

though it is recognised that peptides and proteins can be absorbed from the GIT(11), the bioavailability of therapeutic peptides and proteins administered by this route is too low. However, for the majority of peptide and protein drugs, oral absorption is limited by the factors like: degradation in the acidic environment of the stomach, enzymatic degradation in the small and large intestine, low mucosal permeability, rapid small intestinal transit and extensive first pass matabolism by the absorbing membrane and the liver.

The fact that colon has a smaller surface area for absorption is offset by other factors like long colonic transit (20-30 hrs) and high responsiveness of the colonic tissue to absorption enhancer (12,13). The larger residence time, less peptidase activity, natural absorptive characteristics and high response to absorption enhancers make the colon a promising site for the delivery of peptides and protein drugs for systemic absoption. Thus, colonic delivery of analgesics, contraceptive peptides, oral vaccines, insulin, interferon and interleukins were attempted for systemic absorption (14,15). Further, drug targeting to colon has been proved to be useful where intestinal delayed drug absorption is required as in the treatment of nocturnal asthma(16).

APPROACHES TO COLON SPECIFIC DRUG DELIVERY

The targeting of orally administered drugs to the colon can be accomplished by the approaches mentioned below;

a)Coating with pH dependent polymers: The principle group of polymers utilised for the preparation of colon targeted dosage form has been the Eudragit and more specifically Eudragit L and S. These are anionic polymers which are water impermeable at low pH, but become ionised and dissolve at intestinal pH.

The use of Eudragit-S as a colon targetable coating was first reported in 1982(17). Then 5-amino salicylic acid (5-ASA) containing barium sulphate, coated with Eudragit-S were tested in 8 patients. At the end of 12 hours, 20 tablets were in the stomach and 4 tablets remained in the colon. At the end of 24 hours, all tablets reached the colon and disintegrated(18). This was the basis for the development of 5-ASA compressing a tablet coated with Eudragit-S. In another study, the chitosan microcores were efficiently encapsulated within Eudragit microspheres, forming a multireservoir system, which gave perfect pH dependent release profile (19) with no release in acidic pH.

The development of a colonic delivery capsule (20) to deliver vasopressin using Eudragit NE-30D, Eudragit S-100 and cellulose acetate phthalate (CAP) and granule formulations (21) of fluorouracil using hydroxyl propyl methyl cellulose and enteric coating with Eudragit were reported for colonic delivery.

b) Time released dosage forms: Small intestinal transit time is relatively constant and is hardly infuenced by the nature of formulation administered. An extension of the use of pH dependent polymers was the use of Pulsincap® system(22). The delivery system consists of a capsule, half of which is nondisintegrating and other half enteric coated. The enteric coat dissolves on entering the small intestine as a hydrogel plug, stoppering the nondisintegrating parts, swells at a rate determined by the degree of cross linking. After a predetermined time (eg.5 hrs), the hydrogel plug swells so much that it is ejected from the nondisintegrating bottom, half of the capsule thereby releasing the drug. It must be noted that the swelling of the hydrogel plug is pH independent. Various scien-

tists (23-25) have attempted to develop pH dependent time released system. Osmotic pumps for colon specific drug delivery (26) and used of transdermal nicotine for ulcerative colitis (27) were also reported. The preparation and evaluation of a time controlled release, ethyl cellulose capsule, composed of 4 parts as drug container, swellable substances (hydroxy propyl cellulose), capsule body, EC for colon trageting are described using fluorescein as a model drug (28) and was concluded that the lag time of the system can be used for the colon delivery of drugs.

c) Delivery system based on the metabolic activity of colonic bacteria: Colonic bacteria carry out a variety of metabolic reactions (29) and the most important of them are reduction and hydrolysis. Different strategies were used to target drugs to the colon based on these actions as described below,

i)Coating with biodegradable azo polymers: The intestinal microflora have a large metabolic capacity and it appears that reduction af azo bonds is a general reaction of colonic bacteria. Vanden Mooter et al.(29) investigated the degradation of different types of azo polymers by colonic bacteria. Azo-linked polymeric prodrugs of mesalamine were prepared and evaluated in simulated human intestinal microbial ecosystem and azo containing polyamides were synthesized and studied in a reductase buffer and in a bioreaction medium (31). For colon targeting of ibuprofen poly(ethyl-ester) azo polymers were synthesized and capsules containing ibuprofen were coated with 5, 10 or 15% PEG 400, release was measured in a suspension of rat cecal content in phosphate buffer (pH 6.8) and in plain phosphate buffer (32). Drug release was higher in rat cecal content than in phosphate buffer and resulted in a higher release of ibuprofen. Hydrogels have been produced

based on acrylamide and N-terbutyl acrylamide cross linked with azo aromatic compounds(33).

ii)Prodrug: Corticosteroid prodrugs have been developed (34) by the attachment of the active agent to glycosidic carriers. A comprehensive review on in vivo performance of these agents have been published (35). Colon specific prodrug sulfasalazine is used in the treatment of ulcerative colitis and Crohn's disease. Chemically sulfasalazine is 5-ammosalicylic acid with sulphapyridine by azo bonding. On reaching the colon, the azo bond is reduced by colonic azo reductase to 5-ASA and sulphapyridine. The active moiety is 5-ASA and sulphapyridine simply acts as carrier to deliver 5-ASA intact to the colon. The polymeric prodrug of 5-ASA was also developed by coupling 5-amino group to a spacer group by means of azo bond (36). The production method of certain colon degradable dextran fatty acid esters and their relevant properties as excipients for colon dosage forms were reported.

iii) Hydrogels: The synthesis and characterisation of hydrogels for site specific delivery of peptide and protein drugs to the colon was described by Brownsted et al (37). In the acidic pH of the stomach, the gels have a low degree of swelling, which protects the drug against degradation by enzymes. As the gel passes down the GIT, the degree of swelling increases. On entering the colon, the gel reaches a degree of swelling that makes the cross linking accessible to enzyme or mediator. The cross links are then degraded and the drug is released from the disintegrated gels. Hydrocortison hydrogels prepared from dextran of m.w. 400,000 and 2,000,000, crosslinked with diisocynate, were evaluated for stability, swelling and mechanical strength in vi-

tro, for degration in rats and for drug release (38).

d)Poysaccharides as carriers/coating agents:

A number of delivery systems based on polysaccharides which are selectively degraded in the colon have been reported.

i)Pectin: Amidated pectins were assessed in vitro, for their potential value in colonic drug delivery, by monitoring the release of a model soluble drug acetaminophen(paracetamol), which gives sensitive indication of the behavior of the pectin under simulated gastrointestinal condition(39). The release of a model drug, acetaminophen from tablets that were film coated with a mixture of pectin and ethylcellulose and the potential of the coating as a colonic delivery system were studied(40). The physical properties of mixed pectin+EC film intended for use as a coating agent in colonic drug delivery were studied. Increasing concentration of pectin imparted increasing brittleness and decreasing toughness to the film and did not change the film permeability to moisture.

ii) Chitosan: Core particle composed of theophylline and sodiumtriphosphate that were prepared by agglomeration were uniformely coated with a film of complex of chitosan and triphosphate by suspension coating in liquid and the release of theophylline from the coated particle was studied(41). Chitosan and ethyl cellulose were used as excipients in preparing cephalexin sustained release microcapsules using an emulsion phase separation and coacervation method. Chitosan-alginate microspheres may be used as a vehicle for delayed release of protein drugs for colon specific drug delivery system(42). Guar gum as a carrier for colon specific delivery of indomethcin was studied(43). The ability of polyaspartic acid (poly l-aspartic acid) to act as a drug carrier for the model drug dexamethason was studied in homogenised luminal contents of GI-tract segments of rats to access colon specific drug delivery via enzyme of mircroflora that cleave certain peptide and ester bonds (44). Mesalamine pellets were coated with a mixture of amylose and insoluble polymer and the pellets were evaluated in vitro for potential colon specific delivery(45). Inulin and polygalactomannans were also used as a carrier for colon specific drug delivery system(46).

Conclusions

i) It is now appreciated that the colon can be an important site for the absroption and delivery of drugs. Colon targeted drug delivery system is mostly used for those drugs which are susceptible to the acidic environment of the stomach, enzymatic degradation in the small and large intestine, low mucosal permeability, rapid small intestinal transit and those drugs which undergo extensive first pass metabolism by the absorbing membrane and the liver.

ii) In case of sustained release dosage forms, they spend most of their time within the colon, so the study of colonic drug absorption is important. Although the surface area in the colon is low compared to the small intestine, it is compensated by marked slower rate of transit.

iii) Colon is a promising site for delivery of peptide and protein drugs.

iv) Colon specific drug delivery can be achieved by coating with pH dependent polymers.

v) As the colon contains large population of bacteria, most promising colonic drug delivery systems which are dependent on the enzymatic action of colonic bacteria are those based on polysaccharides. The

polysaccharides are biodegradable, abundantly available and also cheap. Natural polysaccharides such as pectin and xylan are not digested in the human stomach and small intestine, but are degraded by resident bacteria of the colon. The polysaccharides that are under investigation to be used as better carrier for colon specific delivery include pectin and its salt, guargum, chitosan, amylose and chondroitin sulfate.

vi) It has been demonstrated that azo polymers will only be degraded if they are sufficiently hydrophilic. If not, the azo function in the hydrophoblic polymers will undergo a reversible chemical change to form a hydrazine and from the toxicological view point, this could be seen as an advantage, since formulation of low molecular weight degraded products would be avoided.

References

1. Bararow, L., Spiller, R.C. and Wilson, C.G.: Adv. Drug Del. Rev. 7, 201(1991)
2. Metcalf, A.M., Phillips, S.F., Zinsmeister, A.R., Maccart, L., Beart, R.W. and Wolf, B.G.: Gastroenterolgy 92, 40(1987)
3. Hinds, J.P., Stoney, B. and Wold, A.: Am. J. Gastroenterol. 84, 123(1989)
4. Wyman, J.B., Heatin, K.W., Manning, A.P. and Wicks, A.C.B.: Gut 19, 146(1978)
5. Hardy, J.G.: Colonic Transit And Drug Delivery. (In) Hardy, J.G., Davis, S.S. and Wilson, C.G.(Eds.) Drug Delivery To The Gastrointestinal Tract 75 Ellis Horwood, Chichesta 1989
6. Parker, G., Wilson, G.G. and Hardy, J.G.: J.Pharm.Pharmacol. 40, 376 (1988)
7. Cann, P.A., Read, N.W., Brown, C., Hobson, N. and Holdworth, C.D.: Gut 24, 405 (1983)
8. Davis, S.S., Washington, N.,Parr, G.D., Short, A.H., John, V.A., Lloyd, P. and Walker, S.M.: Br. J. Clin. Pharmacol. 26, 435 (1988)
9. Prince, J.M.C., Davis, S.S. and Wilding, I.R.: Int. J. Pharm. 76, 123 (1991)
10. Brunton, L.: Drugs Affecting Gastrointestinal Function (In) Hardman, J.G., Goodman Gilman, A and Limbird, L.E.(Eds.) The Pharmacological Basis Of Therapeutics, Section 6, McGraw Hill, New York 1996
11. Garnder, M.L.G.: Absorption Of Intact Proteins And Peptides (In) Johnson, S.L.R. (Ed.) Physiology Of Gastrointestinal Tract, Chapter 53 Raven Press, New York 1994
12. Digenis, G.A. and Sandefer, E.: Crit. Rev. Ther. Drug Carrier Syst. 7, 309 (1991)
13. Taniguchi, K., Muranishi, S. and Sezaki, H.: Int. J. Pharm. 4, 219 (1980)
14. Saffran, M., Kumar, G.S., Neckers, D.C. et al.: Pharm. Weekbl.Sci. Ed. 10, 159 (1988)
15. Mackay, M. and Tomlinson, E.: Colonic Delivery Of Therpeutic Peptides And Proteins (In) Bieck, P.(Ed.) Colonic Drug Absorption And Metabolism 159 Marcel Dekker, New York 1993
16. Quadros, E., Cassidy, J., Hirschberg, Y. et al.: STP Pharma. Sci. 5,77 (1995)
17. Dew, M.J., Hughes, P.T., Lee, M.G., Evans, B.K. and Rhodes, J.: Br. J. Clin. Pharmac. 14, 405 (1982)
18. Dew, M.J., Ryder, R.E.J., Evans, N., Evans, B.K. and Rhodes, J.:Ibid. 19, 185 (1983)
19. Lorenzo-Lamosa, M.L., Ramunam-Lopen, C., Vila-Jato, J.L. and Alonso, M.J.: J. Controll. Rel. 52, 109 (1998)
20. Arshady, R.: Ibid. 17, 1 (1991)
21. Ciftci, K. and Groves, M.J.: Int. J.Pharm. 145, 157 (1996)
22. Muranishi, S., Yoshikawa, H. and Sezaki, H.: J. Pharmacobio. Dyn. 2, 286 (1979)
23. Pozzi, F.; Furlani, P., Gazzaniga, A., Davis, S.S. and Wilding, I.R.: J. Controll. Rel. 31, 99 (1994)
24. Gazzaniga, A., Giordana, F., Sangalli, M.E. and Zema, L.: STP Pharma. Sci. 4, 336 (1994)
25. Theeuwes, F., Wong, P., Burkoth, T.L. and Fox, D.A.: Osmotic System For Colon Targeted Drug Delivery (In) Bieck, P.(Ed.) Colonic Drug Absorption And Metabolism, Chapter 7, Marcel Dekker, New York 1993
26. Guslandi, M. and Tittobello, A.: Ann-Intern-Med. 492, 127 (1997)
27. Niwa, K., Takaya, T., Morimoto, T. and Takada, K.: J.Drug Target. 3,83(1995)
28. Hardy, J.G., Lee, S.W., Clark, A.G. and Reynolds, J.R.: Int. J. Pharm. 31, 151 (1986)
29. Vanden Mooter, G., Samyn, C., Kinget, R.: Ibid. 97, 133 (1993)
30. Gavart, A., Kanaway, E.R., Molly, K., Gelan, J., et. al.: J. Controll. Rel. 39, 327 (1996)
31. Kalala, W., Kinget, R.L., Vanden Mooter, G., Samyn, C.: Int. J. Pharm. 139, 187 (1996)

32. Kopecek, J., Kopeckova, P., Brondsted, H., Rathi, R., Rihova, B., Yeh, P.Y., Ikesue, K.:J.Controll. Rel. 19, 221 (1992)

33. Friend, D.R., Chang, G.W.: J.Med. Chem. 27, 261 (1984)

34. Friend, D.R., Tozer, T.N.: J. Controll. Rel. 19, 109 (1992)

35. Schacht, E., Callant, D., Verstrasct, W.: Proc.Int. Symp. Controll. Rel. Bioact. Mater. 18, 686 (1991)

36. Kesselhut, J.F., Bauer, K.H.: Pharmazie 550, 263 (1995)

37. Brownsted, H. Kopeck, J.: Biomaterials 12, 584(1991)

38. Hovgaard, L., Bronsted, H.: J. Controll. Rel. 36, 159 (1995)

39. Rubinstein, A., Radai, R., Ezra, M., Pathatka, S., Rokea, J.S.: Pharm. Res. 10, 258 (1993)

40. Wakerly, Z., Fell, J., Attwood, D., Parkins, D.: J.Pharm. Pharmacol. 49, 622 (1997)

41. Macleod, G.S., Fell, J.T., Collett, J.H.:Int. J.Pharm. 157, 53 (1997)

42. Ding, Y.H.: Chin. J. Pharmaceaticals 27, 494 (1996)

43. Polk, A., Amsden, B., De Yao, K., Peng, T., Goosen, M.F.A.: J. Pharm. Sci. 83, 178 (1994)

44. Rama Prasad, Y.V., Krishnaiah, Y.S. Satynarayana, S.: J. Controll. Rel. 51, 281 (1998)

45. Leopoid, C.S., Friend, D.R.: Int. J.Pharm. 126, 139 (1995)

46. Milojevic, S., Newton, J.M., Cummings, J.H., Gibson, G.R., Allwood, M.C. et al.: J.Controll. Rel. 38, 75 (1996)