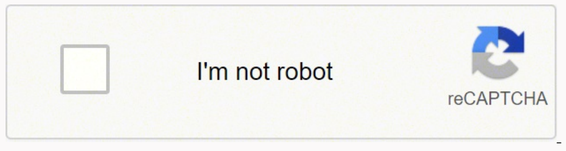

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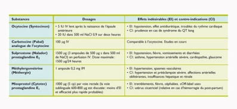

Gastrointestinal drugs pdf. Drugs used in gastrointestinal disorders ppt.

The upper GI tract consists of the mouth, pharynx, esophagus, stomach, and the first part of the small intestine (duodenum), whereas the lower GI tract includes the other parts of the small intestine (jejunum and ileum) and the large intestine (cecum, colon, and rectum) (Marieb and Hoehn, 2010; Reinus and Simon, 2014). Challenges and Recent Progress in Oral Drug Delivery Systems for Biopharmaceuticals. C., Trotman, I. A., Cummings, J. Gastrointestinal transit and systemic absorption of captopril from a pulsed-release formulation. Nanomed. In vitro and in vivo evaluation of an oral system for time and/or site-specific drug delivery. This avoids the limitations of single-unit dosage forms. The effect of surface charge on oral absorption of polymeric nanoparticles. doi: 10.1023/A:1011002913601CrossRef Full Text | Google Scholar Atuma, C., Strugala, V., Allen, A., Holm, L. Gut 38 (6), 859–863. J., Meulbroek, J. Drug delivery to the upper small intestine window using gastroretentive technologies. H. doi: 10.1016/j.jconrel.2013.07.031PubMed Abstract | CrossRef Full Text | Google Scholar Watts, P. J., Kane, J. T., Wang, Y. Control Release 97 (1), 31–42. For example, one of the first formulations of this type was Pulsincap® (Wilding et al., 1992; Stevens et al., 2002; Jain et al., 2011; Patel et al., 2011). doi: 10.1038/nmat2859PubMed Abstract | CrossRef Full Text | Google Scholar Xiao, B., Merlin, D. However, further in vivo studies are required to determine the translatability of these platforms for clinical use. Variability in gastric emptying time can also affect drug release in the small intestine (Al-Gousous et al., 2017). For example, mannose receptors are localized on the apical surface of enterocytes (Fievez et al., 2009; Managuli et al., 2018). Improved intestinal absorption of calcitonin by mucoadhesive delivery of novel pectin–liposome nanocomplexes. doi: 10.1007/BF02093613CrossRef Full Text | Google Scholar Lin, H. Evidence does not support absorption of intact solid lipid nanoparticles via oral delivery. Variation in gastrointestinal transit of pharmaceutical dosage forms in healthy subjects. doi: 10.1084/jem.184.3.1045PubMed Abstract | CrossRef Full Text | Google Scholar Gareb, B., Eissens, A. doi: 10.1023/A:1015849700421CrossRef Full Text | Google Scholar Cummings, J. M., Richter, J. The ethyl cellulose granules then ensure time-dependent drug release in the colon. doi: 10.1023/A:1018893409596CrossRef Full Text | Google Scholar Fievez, V., Plapied, L., des Rieux, A., Pourcelle, V., Freichels, H., Wascotte, V., et al. 43 (2-3), 207–223. This should be taken into account to avoid an overestimation of the nanoparticle transport capacity in humans (Lundquist and Artursson, 2016).Nanoparticulate Dosage Forms for Colon DeliveryThe use of nanoparticulate formulations have demonstrated promising results for colonic drug delivery (Hua, 2014; Hua et al., 2015; Zhang et al., 2017). Therefore, changes in intestinal fluid volumes can influence the way conventional formulations are processed in the GI tract.Gastrointestinal Enzymes and MicrobiomeEnzymatic and microbial degradation of drugs and dosage forms can occur throughout the GI tract. 42 (5), 445–451. It should be noted that there have been conflicting results on the effect of surface charge on colonic targeting, with results mainly based on ex vivo tissue binding studies or in vivo studies following rectal administration (Hua et al., 2015). Controlled Release 130 (2), 154–160. Y., Reddy, M. doi: 10.1093/glycob/cwp048PubMed Abstract | CrossRef Full Text | Google Scholar Lautenschlager, C., Schmidt, C., Lehr, C. 58 (9), 2594–2598. doi: 10.1038/nrgastro.2013.35PubMed Abstract | CrossRef Full Text | Google Scholar Joshi, G., Kumar, A., Sawant, K. Colonic transit is typically faster in IBD patients and is likely due to diarrhea, which is typically worse during active disease (Hebden et al., 2000; Podolsky, 2002). doi: 10.3390/pharmaceutics11040193CrossRef Full Text | Google Scholar Umamaheshwari, R. K., Gangarosa, L. doi: 10.1021/nn502754cPubMed Abstract | CrossRef Full Text | Google Scholar Homayun, B., Lin, X., Choi, H. Nanotechnol. 25 (4-5), 455–465. The small intestine microbiota, nutritional modulation and relevance for health. B., Verma, S. E., Kumar, P., du Toit, L. Amoxicillin, clarithromycin, and omeprazole based targeted nanoparticles for the treatment of H. Appl. Major ligands that have been conjugated to the surface of nanoparticles for targeting Peyer's patches include mannose receptor binding ligands (Fievez et al., 2009; Singodia et al., 2012; Youngren et al., 2013; De Coen et al., 2016), lectin-based ligands (Foster et al., 1998; Clark et al., 2000; Clark et al., 2001; Manocha et al., 2005; Chionh et al., 2009), and integrin specific ligands (Frey et al., 1996; Fievez et al., 2009). Dual TNF-alpha/Cyclin D1 Gene Silencing With an Oral Polymeric Microparticle System as a Novel Strategy for the Treatment of Inflammatory Bowel Disease. H., Jepson, M. R., Mulik, R., Jun, B., Hoffmann, P. 22 (24), 7573–7577. This promotes the slow release of drug in the stomach, which subsequently extends the time available for drug dissolution and absorption in the stomach and/or small intestine. For example, increased colonic motility in diarrhea can lead to reduced retention of locally acting dosage forms and incomplete drug release (Watts et al., 1992). Gut reaction: impact of systemic diseases on gastrointestinal physiology and drug absorption. Development and Characterization of Gastroretentive High-Density Pellets Lodged With Zero Valent Iron Nanoparticles. Colloids Surf B Biointerf. These enzymes can affect the stability of susceptible drugs and dosage forms, but they can also be exploited in formulation design for regional drug delivery in the GI tract.Table 1 Main enzymes in the gastrointestinal tract.The intestinal microbiome, which contains over 500 distinct bacterial species (Sartor, 2008; Consortium, 2012), is also important for both digestion and intestinal health, including digestion and metabolism of carbohydrates, fatty acids, and proteins (Macfarlane and Macfarlane, 2011) (Figure 1). Each granule is coated with Eudragit® L, which is a pH-dependent coating that dissolves at pH >5.5 to allow drug release in the ileum and ascending colon. Biopharm. For example, gastric emptying time can be significantly prolonged after eating, which can lead to premature drug release in the small intestine instead of the colon (Ibekwe et al., 2008; Reinus and Simon, 2014). The small intestine has only one type of mucus that is unattached and loose (Atuma et al., 2001; Johansson et al., 2013). Chemical modification of polysaccharides or combining them with other conventional hydrophobic polymers have been investigated as a way to increase their hydrophobicity. Gut 29 (8), 1035–1041. Control Release 183, 167–177. (2006b). In addition, assessment against proper controls, including the gold standard treatment and not just free drug solution, is required to determine the potential place in therapy of the innovative platform (Hua et al., 2018). doi: 10.1517/17425247.5.6.681PubMed Abstract | CrossRef Full Text | Google Scholar Kang, J. The main parameters are particle size, nanoparticle composition, and surface modification. The effect of chitosan on transcellular and paracellular mechanisms in the intestinal epithelial barrier. A., Blair, H., Liang, L., Brey, R. Today 3 (6), 198–204. 50 (6), 989–1004. doi: 10.1016/j.ejpb.2009.04.009PubMed Abstract | CrossRef Full Text | Google Scholar Fonte, P., Nogueira, T., Gehm, C., Ferreira, D., Sarmento, B. Its primary function is to process the waste products and absorb any remaining nutrients and water back into the system, which is important for homeostasis (Reinus and Simon, 2014). doi: 10.1097/MCG.0b013e31822fecfePubMed Abstract | CrossRef Full Text | Google Scholar Macfarlane, G. E., Maroni, A., Zema, L., Busetti, C., Giordano, F., Gazzaniga, A. 20 (9), 998–1008. Colonic transit times can be highly variable, with ranges from 6 to 70 h reported (Coupe et al., 1991; Rao et al., 2004). Recent technologies in pulsatile drug delivery systems. 92 (5), 1085–1094. Mechanisms of nanoparticle internalization and transport across an intestinal epithelial cell model: effect of size and surface charge. doi: 10.1021/mp9000926PubMed Abstract | CrossRef Full Text | Google Scholar Tobio, M., Sanchez, A., Vila, A., Soriano, I. doi: 10.1016/j.ijpharm.2018.06.054PubMed Abstract | CrossRef Full Text | Google Scholar Hatton, G. 501 (1-2), 18–31. 64 (1), 37–46. (2014b). Sports Med. Lysosomes are intracellular vesicles with an acidic pH of 4.5–5 (Mindell, 2012) and contain a variety of enzymes that have a physiological role in degrading or recycling foreign molecules or cellular compounds (Saftig and Klumperman, 2009). Expert Rev. Effect of dosing time on the total intestinal transit time of non-disintegrating systems. Trans. X., Hsiao, C. doi: 10.1016/j.biomaterials.2008.08.009PubMed Abstract | CrossRef Full Text | Google Scholar Murakami, T. However, when large resections (usually greater than 50%) are performed, there may be profound changes in gastrointestinal function, including motility and drug absorption. For example, nanoparticles can promote enhanced and selective delivery of drugs into inflamed colonic tissue by exerting an epithelial enhanced permeability and retention (eEPR) effect (Collnot et al., 2012; Xiao and Merlin, 2012), as well as allowing preferential uptake by immune cells that are highly increased in inflamed tissue (Lamprecht et al., 2005a). 11 (6), 794–799. A., Zhang, Y., et al. Only a few studies have investigated the effect of surface charge, hydrophobicity, and shape on the bioavailability and absorption of nanoparticles after oral administration. This has been exploited in formulation design with the use of non-starch polysaccharide coatings, which undergo relatively exclusive fermentation by the colonic microbiome (Sinha and Kumria, 2001). Drug Delivery 7 (11), 1291–1301. As fatty acids are the most potent stimulant of the ileal brake, a loss of both fatty acids from digestion and fatty acid receptors from resected tissue lead to a loss of the ileal brake (Lin et al., 2005) and, therefore, cause more rapid intestinal transit and less time for absorption. doi: 10.4103/2230-973X.85969CrossRef Full Text | Google Scholar Patel, M. Control Release 210, 189–197. Human Anatomy and Physiology. In addition, specificity in the site of binding in the small intestine, which is already extensive in length and highly convoluted, is also difficult to predict. Application of a biomagnetic measurement system (BMS) to the evaluation of gastrointestinal transit of intestinal pressure-controlled colon delivery capsules (PCDCs) in human subjects. 18 (3-4), 315–323. L., Faivre, V., Pugh, W. doi: 10.1016/j.ijpharm.2013.01.021PubMed Abstract | CrossRef Full Text | Google Scholar Zhang, J., Tang, C., Yin, C. M., Adrian, T. In general, small resections usually pose minimal issues for oral drug delivery, as the remaining intestine can compensate so that no functionality is lost (Kvietys, 1999; Titus et al., 2013). Ann. Ulex europaeus 1 lectin targets microspheres to mouse Peyer's patch M-cells in vivo. The gastrointestinal mucus system in health and disease. R., Rogers, J. Motil. K., Vyas, S. A., Stevenson, B. R., Misiewicz, J. In addition, coating the surface of nanoparticles with polyethylene glycol (PEG) to create a hydrophilic surface chemistry minimized strong interaction with the mucus constituents and increased particle translocation through the mucus as well as mucosa (Maisel et al., 2015; Du et al., 2018). Very little drug absorption occurs in the stomach owing to its small surface area.The small intestine is the longest (approximately 6 meters in length) and most convoluted part of the GI tract, where digestion is completed with enzymes from the liver and the pancreas, and most of the absorption of nutrients then takes place (Marieb and Hoehn, 2010; Reinus and Simon, 2014). A review on 5-aminosalicylic acid colon-targeted oral drug delivery systems. L. All disease begins in the gut: Influence of gastrointestinal disorders and surgery on oral drug performance. J., Bhalekar, M. doi: 10.4161/biom.1.1.17717PubMed Abstract | CrossRef Full Text | Google Scholar Jain, S., Rathi, V. 13 (12), 1838–1845. Common laboratory animal species have been reported to have significantly higher density of Peyer's patches in the intestine compared to humans (Kararli, 1995). Unpredictable Performance of pH-Dependent Coatings Accentuates the Need for Improved Predictive in Vitro Test Systems. 10 (6), 687–699. E., Gazzaniga, A. Gut 30 (10), 1362–1370. For drug delivery, the mucus layer acts as an important barrier for the permeability of drug molecules (especially hydrophobic molecules) and can also decrease the residence time of drugs and dosage forms.Intestinal Fluid VolumeControl of luminal fluidity is central to gastrointestinal function (Chowdhury and Lobo, 2011; Reinus and Simon, 2014). pylori. In contrast, the stomach and colon have the thickest mucus layer in the GI tract, with a two-layered mucus system comprising of: (i) an inner, attached mucus layer and (ii) an outer, unattached, loose mucus layer (Atuma et al., 2001; Johansson et al., 2013) (Figure 1). High temporal and inter-individual variation detected in the human ileal microbiota. D., Peppas, N. Eng. L., et al. The stomach content is also highly hydrated, which can affect the adhesion of many mucoadhesive polymers (Pawar et al., 2011; Sunoqrot et al., 2017).Initial in vivo biodistribution studies of nanoparticulate dosage forms have demonstrated prolonged gastroretention of up to 3 h in animals that have been fasted (Sarparanta et al., 2012). D., Amiji, M. For example, chitosan (cationic polymer) has been reported to facilitate the paracellular transport of nanoparticles (Zhang et al., 2014a; Liu et al., 2016). H., Doshi, N., Banerjee, A., Anselmo, A. (1992). doi: 10.1080/10611860701733278CrossRef Full Text | Google Scholar Ramteke, S., Ganesh, N., Bhattacharya, S., Jain, N. doi: 10.1016/j.ijpharm.2019.01.022PubMed Abstract | CrossRef Full Text | Google Scholar Shakweh, M., Ponchel, G., Fattal, E. N., Jain, S. 315 (1), 196–202. 494 (1), 49–65. 77 (7), 2962–2970. Google Scholar Reix, N., Parat, A., Seyfritz, E., Van der Werf, R., Epure, V., Ebel, N., et al. J., et al. 49 (4), 712–722. 229 (1-2), 155–162. T., Panda, A. doi: 10.1016/j.jconrel.2019.01.023PubMed Abstract | CrossRef Full Text | Google Scholar Vita, A. doi: 10.1111/j.1365-2982.2012.01953.xPubMed Abstract | CrossRef Full Text | Google Scholar Griffin, B. Comparative pharmacokinetic study of a floating multiple-unit capsule, a high-density multiple-unit capsule and an immediate-release tablet containing 25 mg atenolol. R., Zara, G. doi: 10.1016/j.ejps.2013.04.031CrossRef Full Text | Google Scholar Tariq, M., Alam, M. Effective translation will depend on rational dosage form design to enable improvements in gastrointestinal drug delivery for the treatment of both systemic diseases and local gastrointestinal diseases.Author ContributionsSH was involved in conception of the idea for the review, drafted the manuscript, and approved the final version of the manuscript.Conflict of InterestThe author declares that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.AcknowledgmentsThe author wishes to thank the University of Newcastle, Pharmacy Research Trust of New South Wales, Rebecca L. M., Meuwissen, S. K., Huijsdens, X. doi: 10.1016/j.ijpharm.2012.08.024PubMed Abstract | CrossRef Full Text | Google Scholar Rosenthal, R., Gunzel, D., Finger, C., Krug, S. Therefore, they remain an important challenge in formulation design.Impact of Disease on Oral Drug DeliveryDepending on disease severity, gastrointestinal pathologies can affect some or all of the physiological variables for oral drug delivery (Hatton et al., 2018). It should be noted that most of these polymers are strongly hydrophilic, which can lead to premature drug release before the colon is reached (Hovgaard and Brondsted, 1996; Van den Mooter, 2006; Patel, 2015). This occurs with the prodrugs of 5-aminosalicylic acid (5-ASA), such as sulfasalazine and olsalazine, which are used in the treatment of IBD (Oz and Ebersole, 2008). For absorption to occur, drugs must be able to penetrate the epithelium, which is the innermost layer that forms a continuous lining of the entire GI tract. Drug Delivery Rev. doi: 10.1136/gut.29.8.1042PubMed Abstract | CrossRef Full Text | Google Scholar Stevens, H. F., Simon, D. Acta Helvetiae 73 (2), 81–87. 15 (5), 745–750. However, further studies are required to determine the optimal nanoparticulate design that provides translatable and reproducible outcomes in humans. In general, delayed orocecal transit times (i.e., the time taken for the meal to reach the cecum) have been reported in IBD patients, except when patients experience dysbiotic conditions (e.g., small intestinal bacterial overgrowth, SIBO) which can be associated with faster transit times (Kashyap et al., 2013; Rana et al., 2013). 94 (7), 1876–1883. Further stability studies are required to determine the in vivo small intestinal bioavailability of these nanoparticles following oral administration. The intestinal lymphatic systemic can be targeted via lacteals, which are lymphatic capillary vessels in the villi of the small intestine (Reinus and Simon, 2014; Managuli et al., 2018). Gastrointestinal transit time through the upper small intestine is rapid, thereby limiting the time available for absorption at this site. Therefore, absorption is favored when the drug molecule is in the non-ionized form, which is much more lipophilic than the ionized form.Oral drug delivery is a significant area of formulation research due to the aforementioned advantages for patients. doi: 10.3748/wjg.v13.i10.1477PubMed Abstract | CrossRef Full Text | Google Scholar Miranda, A., Millan, M., Caraballo, I. PubMed Abstract | Google Scholar IBD encompasses a group of chronic relapsing gastrointestinal diseases. R., Van Someren, R. L., Levy, R. 6 (5), 501–508. B., Dammer, E. However, individuals can exhibit variability in pH ranges, with factors such as dietary intake (i.e., food and fluids) as well as microbial metabolism being major determinants (Ibekwe et al., 2008). For example, gastric transit can range from 0 to 2 h in the fasted state and can be prolonged up to 6 h in the fed state (Reinus and Simon, 2014). C., Mi, F. It should be noted that the pH in the cecum drops just below pH 6 and again rises in the colon reaching pH 6.7 at the rectum (Evans et al., 1988; Sasaki et al., 1997; Nugent et al., 2001). Drug release is influenced by formulation factors such as polymer composition, mucosal adhesive strength, drug concentration, drug release rate, and drug release direction (i.e., unidirectional or bidirectional) (Banerjee and Mitragotri, 2017; Homayun et al., 2019). R., Wu, K. Bioengineering Trans. In addition, considerable loss of biodegradable dosage forms may occur in the case of diarrhea, due to insufficient time for activation or drug release (Sartor, 2010; Albenberg and Wu, 2014).Combination of StrategiesTo circumvent the issues with variability in gastrointestinal physiology, a combination of colon-targeting strategies has been utilized in conventional formulations. doi: 10.1016/S0168-3659(01)00291-7PubMed Abstract | CrossRef Full Text | Google Scholar Sarparanta, M. Surfactant-dependence of nanoparticle treatment in murine experimental colitis. B., Chen, W. Radiol. L., Iqbal, S., Li, H. These factors are known to be more consistent to allow efficient colon-targeted drug delivery. States A. Biodegradable nanoparticles for targeted drug delivery in treatment of inflammatory bowel disease. doi: 10.1016/j.biomaterials.2013.06.008PubMed Abstract | CrossRef Full Text | Google Scholar Xiao, B., Laroui, H., Viennois, E., Ayyadurai, S., Charania, M. The delivery of high drug concentrations in the stomach is particularly beneficial for the treatment of local diseases such as gastritis, gastric ulcer, and bacterial infections (e.g., Helicobacter pylori), as well as for drugs that have better absorption in the stomach (Rouge et al., 1996; Mandal et al., 2016).To address the potential for rapid clearance from the stomach, studies have incorporated gastroretentive strategies to nanoparticulate formulations, especially mucoadhesive (Umamaheshwari et al., 2004; Ramteke et al., 2008; Ramteke and Jain, 2008; Jain et al., 2009; Ramteke et al., 2009; Sarparanta et al., 2012; Ngwuluka et al., 2015; Jain et al., 2016; Sunoqrot et al., 2017) and high-density systems (Ngwuluka et al., 2015; Sharma et al., 2018). This can lead to difficulties in targeting specific regions of the colon with conventional formulations. 106 (Pt B), 242–255. doi: 10.1177/00970002042006005PubMed Abstract | CrossRef Full Text | Google Scholar McConnell, E. The mucoadhesive and gastroretentive properties of hydrophobin-coated porous silicon nanoparticle oral drug delivery systems. Lectin-mediated mucosal delivery of drugs and microparticles. 96 (6), 1527–1536. Nanoscale 8 (13), 7024–7035. Exp. M., Curley, P., Kinvig, H., Hoskins, C., Owen, A. K., Vigh, T., et al. Gastroenterology 144 (5), 967–977. G., Welling, P. In addition, lectins can interact with the carbohydrate residue in the mucus layer of the intestinal epithelium (Irache et al., 1994; Diesner et al., 2012; Cornick et al., 2015; Managuli et al., 2018). 25 (8), 1828–1835. Gastrointestinal persorption and tissue distribution of differently sized colloidal gold nanoparticles. However, disintegration and absorption from formulations containing enteric coatings or pH-responsive matrices may be erratic, due to the relatively slow dissolution or degradation of the polymers in comparison to the transit time of the formulation through the small intestine (Al-Gousous et al., 2017; Kang et al., 2018). In addition to triggering release at a specific pH range, the enteric coating protects the incorporated active agents against the harsh GI tract environment (e.g., gastric juice, bile acid, and microbial degradation) and can create an extended and delayed drug release profile to enhance therapeutic efficiency (Yang et al., 2002; Van den Mooter, 2006). A., Rodriguez-Gascon, A., Muccioli, G. 156, 1–8. doi: 10.1615/CritRevTherDrugCarrierSyst.v13.i3-4.10PubMed Abstract | CrossRef Full Text | Google Scholar Hu, Z., Mawatari, S., Shibata, N., Takada, K., Yoshikawa, H., Arakawa, A., et al. Gut 29 (8), 1042–1051. M-cell targeting of whole killed bacteria induces protective immunity against gastrointestinal pathogens. doi: 10.1016/j.jconrel.2012.03.004PubMed Abstract | CrossRef Full Text | Google Scholar Nugent, S. M., Storm, G. This is particularly beneficial for drugs that have poor solubility in the small intestine or are unstable in the harsh gastric environment (Lundquist and Artursson, 2016). Drug Targeting 16 (1), 65–72. (1993). Design and evaluation of colon targeted modified pulsincap delivery of 5-fluorouracil according to circadian rhythm. doi: 10.1016/j.biomaterials.2013.01.079PubMed Abstract | CrossRef Full Text | Google Scholar Zhang, J., Zhu, X., Jin, Y., Shan, W., Huang, Y. J., Keely, S. T., Allison, C., Gibson, S. doi: 10.1016/j.nano.2015.02.018PubMed Abstract | CrossRef Full Text | Google Scholar Hua, S., de Matos, M. In healthy rats and rats with induced colitis, it was observed that 100 nm particles showed significantly increased accumulation in inflamed colon in comparison to healthy animals (Lamprecht et al., 2001a). Decades of research in drug targeting to the upper gastrointestinal tract using gastroretention technologies: where do we stand? Y., Sood, A. pH-Sensitive nanospheres for colon-specific drug delivery in experimentally induced colitis rat model. Orally administered biodegradable microspheres target the peyer's patches. For example, nanoparticles would need to cross the intestinal epithelium to reach the lamina propria and then traverse a layer of endothelial cells of the blood vessels for systemic delivery. S., Fix, J. E., Tripathi, V., Gupta, S. These were found to be confined to sites of disease and correlated with disease progression (Simmonds et al., 1992; Lih-Brody et al., 1996). Drug Deliv. doi: 10.1023/A:1015118923204CrossRef Full Text | Google Scholar Shreya, A. M., Schumann, M., Bojarski, C., Schulzke, J. In addition, lectins can show nonspecific interactions with the mucus layer of the intestinal epithelium (Irache et al., 1994; Cornick et al., 2015; Managuli et al., 2018) and can have toxicity and stability issues (Zhang and Wu, 2014).Enhancing the transcytosis of intact nanoparticles across enterocytes is a promising strategy to improve the systemic delivery of drugs that have poor stability or solubility in the GI tract. doi: 10.1517/17425247.3.5.583PubMed Abstract | CrossRef Full Text | Google Scholar Goto, T., Tanida, N., Yoshinaga, T., Sato, S., Ball, D. N., Ma, N., Haag, R. Limited exposure of the healthy distal colon to orally-dosed formulation is further exaggerated in active left-sided ulcerative colitis. doi: 10.1208/s12249-013-9988-3PubMed Abstract | CrossRef Full Text | Google Scholar Yu, M., Yang, Y., Zhu, C., Guo, S., Gan, Y. They are also able to protect the drug from degradation during transit in the upper GI tract. Z., Prebeg, Z., Kurjakovic, N. N. 13th edition (New York: McGraw-Hill Education). Peptides that have the capability of modulating the degree and kinetics of tight junctions have also demonstrated enhanced paracellular transport of drugs (Taverner et al., 2015). (2011). Nanoparticles can cross the intestinal epithelium via three main pathways — paracellular transport (between cells through tight junctions), transcellular transport (through the interior of cells with subsequent exocytosis), and M-cell-mediated transport (Yu et al., 2016; Reinholz et al., 2018). However, the absorption of nanoparticles by M cells is limited due to the low proportion of M cells (~1%) in the intestinal epithelium. Therefore, considerations should be made during formulation design to the following factors (Martinez and Amidon, 2002; Hua et al., 2015): (i) how long the formulation resides in specific sections of the GI tract; (ii) the influence of the gastrointestinal environment on the delivery of the formulation at the site of action as well as on the stability and solubility of the drug; (iii) the intestinal fluid volume; and (iv) the degree of metabolism of the drug or formulation in the GI tract through microbial or enzymatic degradation.Figure 1 Physiological factors in the gastrointestinal tract that influence oral drug delivery. In particular, high amounts of eosinophil cationic protein and transferrin have been observed in the inflammatory tissue of the colon in IBD patients (Carlson et al., 1999; Peterson et al., 2002; Tirosh et al., 2009). Drug Discovery 12 (12), 1219–1232. G., Ansel, H. 83 (1), 18–24. However, the advantage of nanoparticulate formulations is the dispersion of the drug across multiple subunits and, therefore, the distribution of multiple subunits throughout the stomach. Res. The benefit of this approach also includes sustained or controlled release drug delivery, which can reduce fluctuations in systemic drug concentrations as well as increase patient compliance to medications by minimizing the number of doses required (Awasthi and Kulkarni, 2016). 235 (1-2), 1–15. A., Pullen, N. A., Yazaki, E., Evans, D. For example, mesalazine used for IBD is commercially available as oral tablets coated with Eudragit L-100 (Mesasal® and Colitofalk®) or Eudragit S (Asacol®).Table 2 Examples of pH-dependent polymer coatings used for colonic targeting.Time-dependent formulations essentially use gastrointestinal transit times as a guide to activate drug release into the colon. Enhanced transferrin receptor expression by proinflammatory cytokines in enterocytes as a means for local delivery of drugs to inflamed gut mucosa. Colon-specific approaches can be applied to single-unit dosage forms (e.g., capsules) that are loaded with nanoparticles or applied to each of the individual nanoparticle subunits. Role of the intestinal microbiota in resistance to colonization by Clostridium difficile. 90 (12), 1927–1936. For example, 10- to 100-fold increase in mucosal ROS concentrations have been reported in biopsies taken from ulcerative colitis patients (Simmonds et al., 1992; Lih-Brody et al., 1996). doi: 10.4155/tde.11.146PubMed Abstract | CrossRef Full Text | Google Scholar Du, X. doi: 10.1124/jpet.105.088146PubMed Abstract | CrossRef Full Text | Google Scholar Lamprecht, A., Yamamoto, H., Takeuchi, H., Kawashima, Y. S., Shin, U. Nano- and microscaled particles for drug targeting to inflamed intestinal mucosa: a first in vivo study in human patients. doi: 10.1080/17460441.2017.1378176CrossRef Full Text | Google Scholar Ngwuluka, N. doi: 10.1007/s10620-005-2694-6CrossRef Full Text | Google Scholar Ling, S. An orally administered redox nanoparticle that accumulates in the colonic mucosa and reduces colitis in mice. Those that have low water solubility may have better capability for drug retention but can suffer from issues with low degradation (Hovgaard and Brondsted, 1996; Shah et al., 2011).Similarly, azoreductase activity of colonic bacteria has been extensively studied for colon-targeting systems, especially in the development of prodrugs (Rafii et al., 1990; Oz and Ebersole, 2008; Marquez Ruiz et al., 2012). doi: 10.1208/pt050232PubMed Abstract | CrossRef Full Text | Google Scholar Vass, P., Demuth, B., Hirsch, E., Nagy, B., Andersen, S. Effect of intestinal resection on human small bowel motility. ;473 (1-2), 203–212. doi: 10.1016/j.ijpharm.2015.08.014PubMed Abstract | CrossRef Full Text | Google Scholar Niebel, W., Walkenbach, K., Beduneau, A., Pellequer, Y., Lamprecht, A. doi: 10.1136/gut.29.8.1035PubMed Abstract | CrossRef Full Text | Google Scholar Fallingborg, J., Christensen, L. Small intestine- and colon-specific smart oral drug delivery system with controlled release characteristic. T., Buri, P., et al. doi: 10.1136/bjsm.2003.006825PubMed Abstract | CrossRef Full Text | Google Scholar Reinus, J. 15 (8), 787–804. doi: 10.1517/17425247.1.1.141CrossRef Full Text | Google Scholar Sharma, A., Goyal, A. 9 (49), 42492–42502. Modeling of drug release from delivery systems based on hydroxypropyl methylcellulose (HPMC). doi: 10.1016/j.jconrel.2012.01.028CrossRef Full Text | Google Scholar Colombo, P., Bettini, R., Massimo, G., Catellani, P. 72 (1), 1–8. doi: 10.1159/000092878CrossRef Full Text | Google Scholar Britton, R. K., Haider, T., Kumar, A., Jain, A. doi: 10.1016/0378-5173(92)90245-WCrossRef Full Text | Google Scholar Whitehead, L., Fell, J. An in vivo comparison of intestinal pH and bacteria as physiological trigger mechanisms for colonic targeting in man. B., Russell-Jones, G. There are several safety issues that need to be assessed for this type of dosage form, including the potential for accumulation of several dosage units in the stomach following multiple administrations, as well as possible occlusion of the esophagus or pylorus (Kagan and Hoffman, 2008).Mucoadhesive and high-density dosage forms for gastroretention have translational limitations. The hydrated layers allow the penetration of colonic bacteria and enzymes, which lead to degradation and drug release within an acceptable duration (Van den Mooter, 2006; Shah et al., 2011). M., Salonen, J. However, in the majority of cases, the specific mechanism of action was not elucidated.The mucosal uptake of intact nanoparticles is the most challenging, as the nanoparticles would need to cross multiple cellular barriers after penetrating the mucus layer (Reinholz et al., 2018). pH-Responsive carriers for oral drug delivery: challenges and opportunities of current platforms. As the small intestine is the target for these nanoparticulate formulations, considerations should also be given to the stability of the nanoparticles during transit in the upper GI tract.M-Cell-Mediated TransportUptake of nanoparticles by M cells (microfold cells), which are mainly localized in Peyer's patches in the small intestine, have become attractive targets for drug delivery. N., Huang, G. Gastrointestinal distribution and in vivo gene transfection studies with nanoparticles-in-microsphere oral system (NiMOS). Technol. The surface area of the small intestine is increased enormously to approximately 200 m2 in an adult owing to the presence of villi and microvilli that are well supplied with blood vessels (Marieb and Hoehn, 2010; Reinus and Simon, 2014). doi: 10.3109/10717544.2010.520354PubMed Abstract | CrossRef Full Text | Google Scholar Peterson, C. Platforms that require complex and/or laborious synthesis procedures generally have limited clinical translation potential, as they can be quite problematic and costly to pharmaceutically manufacture on a large scale. Control Release 172 (1), 62–68. C. The thick mucus layer protects the mucosal tissue from gastric acid in the stomach and also provides a stable environment for the enteric microflora in the colon (Macfarlane et al., 1988; Atuma et al., 2001). When compared to conventional formulations, nanoparticulate formulations have been demonstrated to have improved or similar therapeutic efficacy at lower drug concentrations (Hua et al., 2015).Basic Physicochemical Strategies for Colon DeliveryNanoparticulate formulations have been designed to passively or actively target the colon. In contrast, anionic delivery systems are considered bioadhesive, as they preferentially adhere to inflamed tissue via electrostatic interaction with the higher concentration of positively charged proteins (Lamprecht et al., 2001b; Jubeh et al., 2004; Meissner et al., 2006; Beloqui et al., 2013). Table 1 shows the main enzymes in the saliva, gastric fluid, and intestinal fluid that are important in the metabolism of proteins, fats, and carbohydrates. These dosage forms are limited by the fact that they require sufficient binding with the intestinal wall to avoid being washed away by solid boluses of digested food, gastric and intestinal fluids, or by the continuous secretion and turnover of mucus (Banerjee and Mitragotri, 2017; Homayun et al., 2019). Drug Delivery Formul. The advantages and disadvantages for each of the gastroretentive dosage forms have been discussed above (refer to “Gastroretentive Drug Delivery Systems”).Formulations that have pH-responsive coatings or matrices are particularly beneficial for drugs that are susceptible to degradation by gastric enzymes or by the acidity of the gastric fluid, as well as for drugs that can cause irritation to the gastric mucosa (Rouge et al., 1996; Thakral et al., 2013; Liu et al., 2017). Premature drug release can also occur with the inter- and intra-individual variability in gastrointestinal transit times (Coupe et al., 1991; Watts et al., 1992; Timmermans and Moes, 1994; Rao et al., 2004; Kagan and Hoffman, 2008; Reinus and Simon, 2014; Brunton et al., 2018). For example, the harsh enzymatic environment might be particularly detrimental to lipid-based nanoparticles due to lipolysis (Beloqui et al., 2016; Hu et al., 2016; Shreya et al., 2018). Genetics and environmental interactions shape the intestinal microbiome to promote inflammatory bowel disease versus mucosal homeostasis. Control Release 238, 176–185. doi: 10.2217/nnm.12.31CrossRef Full Text | Google Scholar Jain, S. doi: 10.1002/jps.24365PubMed Abstract | CrossRef Full Text | Google Scholar Hatton, G. Microbiol. L., Khela, M. Consequences of these resections include a shortened bowel that may have associated implications for oral dosage form design. doi: 10.2165/00003088-200443120-00003PubMed Abstract | CrossRef Full Text | Google Scholar El Aidy, S., van den Bogert, B., Kleerebezem, M. Therefore, further formulation design may be needed for effective oral administration.Considerations for Translational DevelopmentSignificant advances in the development of oral formulations to improve the regional targeting of drugs in the GI tract have been reported in the literature. Biomater. For example, mucoadhesive dosage forms can be unpredictable regarding the site of adhesion (including the risk of esophageal binding) and can potentially suffer from elimination due to the high mucus turnover rate in the stomach (Rubinstein and Tirosh, 1994; Streubel et al., 2006b). Preparation and evaluation of lectin-conjugated PLGA nanoparticles for oral delivery of thymopentin. Neurogastroenterol. Nat. Following oral administration, food and pharmaceuticals transit through the esophagus to the stomach, aided by peristaltic contractions. By increasing the bioavailability of drugs into the small intestine, nanoparticles can be designed to: (i) trigger drug release in the lumen for subsequent absorption; (ii) adhere to the mucosal surface for effective drug release and absorption; (iii) enhance mucosal uptake of intact nanoparticles with subsequent drug release for local or systemic absorption; or (iv) enhance mucosal uptake and absorption of intact nanoparticles into the systemic circulation. M., Blackshaw, P. R., Gilley, R. C., Fadda, H. With regard to nanoparticle shape, initial studies have demonstrated higher cellular uptake and transcytosis of rod-shaped nanoparticles compared to sphere-shaped nanoparticles (Banerjee et al., 2016b). These formulations contain a number of separate nanoparticle subunits in which the dose of the drug is distributed across. K., Shin, H. Control Release 119 (3), 339–348. E., Sjovall, H., Hansson, G. Nanomedicine 10 (1), 167–176. Interestingly, initial studies in humans with IBD demonstrated that microparticles (3 μm) had better bioadhesion and accumulation in the inflamed rectal mucosal wall as well as less propensity for systemic absorption (Schmidt et al., 2013). However, oral administration of antibody and peptide-based formulations can suffer from degradation by gastric acid and enzymes in the GI tract. C., Wang, X. For example, they should consist of components that are biodegradable or can undergo disintegration to smaller components after a predetermined time period. T., Weltzin, R., Giannasca, P. This multiparticulate formulation is indicated for colonic inflammation, particularly for IBD (McKeage and Goa, 2002; Edsbacker and Andersson, 2004). Bioorg. 12, 3213–3227. Incorporation of additional strategies may be required to protect nanoparticles from premature degradation in the GI tract (Makhlof et al., 2011a).The effect of physicochemical parameters, other than particle size, is only beginning to be understood. Biotinylated liposomes as potential carriers for the oral delivery of insulin. doi: 10.2147/ijn.s34105CrossRef Full Text | Google Scholar Manocha, M., Pal, P. 25 (4), 451–523. V., Merlin, D. The colon has been investigated as a site for both systemic and local drug delivery. Biomaterials 33 (11), 3353–3362. Measurement of gastrointestinal transit. Nanoparticles (250 nm), however, were translocated to the serosal compartment of IBD patients, possibly leading to systemic absorption (Schmidt et al., 2013). M., Fischer, D., Stallmach, A. Daidzein-phospholipid complex loaded lipid nanocarriers improved oral absorption: in vitro characteristics and in vivo behavior in rats. In addition, nanoparticles are able to avoid rapid carrier elimination that occurs in diarrhea, as these smaller particles are readily taken up into inflamed tissue and cells (Beloqui et al., 2013). The mucosa of the colon is smooth and has no specialized villi, hence the surface area is vastly smaller than the small intestine (Marieb and Hoehn, 2010; Reinus and Simon, 2014). H., Patel, C. Mucosal inflammation in IBD causes pathophysiological changes, such as: (i) increased mucus production; (ii) a disrupted intestinal barrier due to the presence of mucosal surface alterations, ulcers, and crypt distortions; and (iii) infiltration of immune cells (e.g., macrophages, lymphocytes, neutrophils, and dendritic cells) (Li and Thompson, 2003; Antoni et al., 2014). Anti-Helicobacter pylori effect of mucoadhesive nanoparticles bearing amoxicillin in experimental gerbils model. Nanoparticles in inflammatory bowel disease: particle targeting versus pH-sensitive delivery. doi: 10.1039/C5BM00187KPubMed Abstract | CrossRef Full Text | Google Scholar Hillyer, J. T., Collett, J. Nanomedicine 8 (4), 468–477. (2005b). doi: 10.1038/ctg.2011.1PubMed Abstract | CrossRef Full Text | Google Scholar Kshirsagar, S. B Mater. The main disadvantage of high-density dosage forms is that they can be technically difficult to manufacture, generally requiring a large amount of drug due to the progressive decrease in the weight of the matrix as the drug gets released (Rouge et al., 1998; Awasthi and Kulkarni, 2016).Regional Drug Targeting in the Small IntestineRegional targeting of drugs to the small intestine is usually attained with gastroretentive dosage forms, pH-dependent dosage forms, or mucoadhesive dosage forms. doi: 10.2174/1872211312666180308150218CrossRef Full Text | Google Scholar Lahner, E., Annibale, B., Delle Fave, G. Nanoparticle toxicity by the gastrointestinal route: evidence and knowledge gaps. K., Diwan, P. Pharmacokinetics of budesonide (Entocort EC) capsules for Crohn's disease. Vaccine-containing biodegradable microspheres specifically enter the gut-associated lymphoid tissue following oral administration and induce a disseminated mucosal immune response. Control Release 58 (2), 215–222. This, in turn, can alter microbial metabolism in the GI tract and affect the secretion of enzymes. Intestinal luminal pH in inflammatory bowel disease: possible determinants and implications for therapy with aminosalicylates and other drugs. PubMed Abstract | CrossRef Full Text | Google Scholar Kriegel, C., Amiji, M. doi: 10.1016/j.colsurfb.2017.05.005CrossRef Full Text | Google Scholar Talaei, F., Atyabi, F., Azhdarzadeh, M., Dinarvand, R., Saadatzadeh, A. This includes the following: (i) drugs that act as prokinetics to stimulate gastrointestinal motility (e.g., metoclopramide, domperidone, and cisapride); (ii) drugs that can cause constipation (e.g., opioids, anticholinergic agents, antidiarrheal agents, antacids containing aluminium or calcium, iron/calcium supplements, diuretics, verapamil, and clonidine); and drugs that can cause diarrhea (e.g., laxatives, antibiotics, colchicine, cytotoxic agents, digoxin, magnesium, NSAIDs, orlistat, acarbose, and metformin). doi: 10.1007/s10350-006-0847-0PubMed Abstract | CrossRef Full Text | Google Scholar Camenisch, G., Alsenz, J., van de Waterbeemd, H., Folkers, G. (2011b). The transit rate of different-sized model dosage forms through the human colon and the effects of a lactulose-induced catharsis. F., Carbon, R. doi: 10.1053/j.gastro.2009.11.003PubMed Abstract | CrossRef Full Text | Google Scholar Laroui, H., Geem, D., Xiao, B., Viennois, E., Rakhya, P., Denning, T., et al. Proc. S., Perkins, A. Strategies for targeted drug delivery in treatment of colon cancer: current trends and future perspectives. doi: 10.1016/S0939-8600(02)80002-5CrossRef Full Text | Google Scholar Gazzaniga, A., Maroni, A., Sangalli, M. Nanoparticles generally undergo cellular uptake via the transcellular pathway in the GI tract (Yu et al., 2016; Reinholz et al., 2018). 50, 435–439. Swellable matrices for controlled drug delivery: gel-layer behaviour, mechanisms and optimal performance. (Lond) 7 (9), 1311–1337. Drug absorption sites in the gastrointestinal tract and dosage forms for site-specific delivery. Particle uptake by Peyer's patches: a pathway for drug and vaccine delivery. J., Preat, V. 1 (3), 172–181. Drug Discovery Today 22 (8), 1224–1232. doi: 10.1016/j.ijpharm.2013.05.017PubMed Abstract | CrossRef Full Text | Google Scholar Beloqui, A., Coco, R., Memvanga, P. Formulations can also be designed to enhance drug delivery to specific regions in the upper or lower GI tract. Improvement of oral efficacy of Irinotecan through biodegradable polymeric

nanoparticles through in vitro and in vivo investigations. G. doi: 10.1002/JLB.3MIR1118-414RRCrossRef Full Text | Google Scholar Vong, L. Enhanced mucosal and systemic immune response with intranasal immunization of mice with HIV peptides entrapped in PLG microparticles in combination with Ulex Europaeus-I lectin as M cell target. doi:
10.1016/S1461-5347(00)00269-8CrossRef Full Text | Google Scholar Coupe, A. In general, nanoparticles larger than 5 μm are taken up by M cells but remain entrapped in Peyer's patches, whereas those smaller than 1 μm are taken up by M cells and transported through the efferent lymphatics within macrophages (Eldridge et al., 1989; Eldridge et
al., 1990; Managuli et al., 2018). L., Every, A. Gastroenterology 146 (6), 1547–1553. 440 (1), 3–12. Oral bioavailability enhancement of a hydrophilic drug delivered via folic acid-coupled liposomes in rats. Crit. C., Modi, G., Pillay, V. P. 96 (10), 2746–2756. Drug-loaded nanoparticles targeted to the colon with polysaccharide hydrogel reduce colitis in a
mouse model. Effective oral delivery of insulin in animal models using vitamin B12-coated dextran nanoparticles. (1989). K., Sinha, S. Drug release is also influenced by formulation factors related to the polymer (e.g., composition, concentration, distribution, viscosity) and drug (e.g., loading, solubility, particle size) (Siepmann and Peppas, 2001;
Miranda et al., 2007; Caraballo, 2010).The main disadvantage of this approach is the huge variability seen in gastrointestinal transit time in the stomach, small intestine, and colon—with many physiological, pathophysiological, and pharmaceutical factors influencing these parameters (refer to sections Physiological Factors Influencing Oral Drug
Delivery and Pathophysiological Factors Influencing Oral Drug Delivery). Getting into the colon: approaches to target colorectal cancer. doi: 10.1016/j.xphs.2018.06.014PubMed Abstract | CrossRef Full Text | Google Scholar Sharpe, L. B., Ucakar, B., des Rieux, A., Preat, V. These can affect the performance of locally acting dosage forms. T., Wee, J.
doi: 10.1080/10717544.2017.1279238PubMed Abstract | CrossRef Full Text | Google Scholar Lundquist, P., Artursson, P. Drug Delivery 24 (1), 569–581. In particular, nanoparticulate dosage forms have shown promising results in drug delivery compared to conventional single-unit dosage forms. The bacterial flora in inflammatory bowel disease:
current insights in pathogenesis and the influence of antibiotics and probiotics. doi: 10.1016/j.drudis.2017.05.006PubMed Abstract | CrossRef Full Text | Google Scholar Bannunah, A. 29 (12), 1219–1229. L., Knollmann, B. Metabolism of foreign compounds by gastrointestinal microorganisms. Natl. E., Eggleston, I. L., Ng, G. Drugs administered via the
oral route, however, generally have slower absorption, which is not preferred during an emergency (Homayun et al., 2019). J., Silk, D. U., Ford, A. (2003). 3 (5), 583–597. M., Drossman, D. Biomed. 2 (11), 1499–1508. 6 (4), 1083–1091. Front. For example, sulfasalazine has low absorption in the upper GI tract and is cleaved by azoreductases of the
microflora in the colon to release the active 5-ASA moiety, which is thought to have local actions in the colon. Drug Delivery 23 (9), 3492–3504. A major issue is the rapid passage of nanoparticles through the stomach to the intestine due to their small particle size (Sarparanta et al., 2012). Differences in the anatomy and/or physiology of the animal
species used in in vivo studies compared to humans should also be taken into account when evaluating new formulations (Kararli, 1995; Hatton et al., 2015). Invest. (2009). 6 (3), 642–650. Patient preferences between surgical and medical treatment in Crohn's disease. Suppl. N., Brayden, D., Hirst, B. (2000). Systems for region selective drug delivery
in the gastrointestinal tract: biopharmaceutical considerations. This can affect the composition and diversity of bacterial species and, therefore, the secretion of enzymes that are important in triggering drug release for microbial-dependent drug delivery systems. (2016b). doi: 10.1016/j.biomaterials.2005.03.005PubMed Abstract | CrossRef Full Text |
Google Scholar Liu, M., Zhang, J., Zhu, X., Shan, W., Li, L., Zhong, J., et al. doi: 10.1002/jps.2600830106PubMed Abstract | CrossRef Full Text | Google Scholar Tirosh, B., Khatib, N., Barenholz, Y., Nissan, A., Rubinstein, A. Targeting nanoparticles to M cells with non-peptidic ligands for oral vaccination. doi: 10.1039/c3tb21564dCrossRef Full Text |
Google Scholar Yang, L., Chu, J. Triple therapy-based targeted nanoparticles for the treatment of Helicobacter pylori. (2012). The targeting of surface modified silica nanoparticles to inflamed tissue in experimental colitis. Current Trends and Challenges in the Clinical Translation of Nanoparticulate Nanomedicines: Pathways for Translational
Development and Commercialization. T., Thomas, B. 11 (6), 901–915. Stress and the gut: pathophysiology, clinical consequences, diagnostic approach and treatment options. Both are considered distinct conditions, however, they can display many similar clinical features and typically result in cycles of remitting and relapsing inflammation of the
mucosal tissue. 38 (4), 482–487. 556, 258–265. Control Release 31, 181–188. H., Hwang, J. M., Makila, E. In vitro study of lectin-latex conjugates for specific bioadhesion. 2, e2. K., Gilley, R. Drug diffusion front movement is important in drug release control from swellable matrix tablets. I., et al. Respiratory burst activity of intestinal macrophages in
normal and inflammatory bowel disease. Drug Targeting 16 (9), 694–705. Nanoparticles as potential oral delivery systems of proteins and vaccines: a mechanistic approach. Dev. 6 (4), 317–324. Many IBD patients also undergo surgical resection of intestinal tissues (Byrne et al., 2007). Control Release 20161 (2), 235–246. Control Release 111 (1-2), 1–
18. The terminal ileum is also responsible for bile salt reabsorption and, when removed, can become problematic and is generally manifested by choleretic diarrhea (Titus et al., 2013) that can significantly affect the therapeutic efficacy of conventional oral formulations.Conventional Oral Drug Delivery ApproachesThe main formulations used for oral
drug delivery are liquid dosage forms (such as solutions and suspensions) and solid dosage forms (such as tablets and capsules) (Allen et al., 2011). doi: 10.1002/bdd.2510160502PubMed Abstract | CrossRef Full Text | Google Scholar Kashyap, P. doi: 10.1517/17425247.2010.528199CrossRef Full Text | Google Scholar Carlson, M., Raab, Y., Peterson,
C., Hallgren, R., Venge, P. M., Horava, S. C., El-Aidy, S., Rajilic-Stojanovic, M., Heilig, H. S., Dalmasso, G., Wang, L., Sitaraman, S. For example, surgery is one of the main treatments for colorectal cancer which is defined as the development of malignant cells in the colonic epithelium (Patel, 2014; Banerjee et al., 2017). doi:
10.1021/mp8002539PubMed Abstract | CrossRef Full Text | Google Scholar Jain, D., Raturi, R., Jain, V., Bansal, P., Singh, R. It is generally accepted that a diameter >15 mm is required for prolonging gastric retention, especially during the fasted state (Timmermans and Moes, 1993; Bardonnet et al., 2006). 45 Suppl, S120–S127. This epithelial cell
barrier selectively regulates transport from the lumen to the underlying tissue compartment. (2010). doi: 10.1039/C5NR07474FPubMed Abstract | CrossRef Full Text | Google Scholar Hua, S., Marks, E., Schneider, J. Although there have been an extensive number of studies in the literature on gastroretentive dosage forms, the clinical translation of
these technologies has not progressed as rapidly. D., Dharanivasan, G., Murugesan, R., Verma, R. K., et al. The small intestinal microbiota (El Aidy et al., 2015) is predominantly composed of subject-specific genera such as Clostridium, Escherichia, and Turicibacter in variable amounts. Biopharm 73 (1), 16–24. D., Basit, A. Recent advances in chitosan-
based nanoparticles for oral delivery of macromolecules. Size-Dependent Bioadhesion of Micro- and Nanoparticulate Carriers to the Inflamed Colonic Mucosa. doi: 10.1053/j.gastro.2014.01.058PubMed Abstract | CrossRef Full Text | Google Scholar Al-Gousous, J., Tsume, Y., Fu, M., Salem, I. doi: 10.3390/pharmaceutics11030129CrossRef Full Text |
Google Scholar Hoque, K. Objective evaluation of small bowel and colonic transit time using pH telemetry in athletes with gastrointestinal symptoms. Commonly used targeting moieties include peptides and monoclonal antibodies, which have been shown to have high targeting specificity and potential mucopenetrative properties (Saltzman et al.,
1994). Fab'-bearing siRNA TNFalpha-loaded nanoparticles targeted to colonic macrophages offer an effective therapy for experimental colitis. E., Bloom, S. doi: 10.1111/j.1572-0241.2002.05837.xPubMed Abstract | CrossRef Full Text | Google Scholar Prajapati, J. Bioavailability enhancement, Caco-2 cells uptake and intestinal transport of orally
administered lopinavir-loaded PLGA nanoparticles. (2001). Mucus secretion acts as a lubricant to facilitate the passage of digestive matter and to protect the underlying epithelium from pathogens and mechanical stress (Atuma et al., 2001). E., Stevens, T. Lectin-modified solid lipid nanoparticles as carriers for oral administration of insulin. Drugs 62
(15), 2263–2282. 3 (2), 277–290. In particular, resection of the terminal ileum alters water absorption and dilutes residual bile acids in the colon, thereby reducing net colonic fatty acid concentrations (Thompson et al., 1998; Gracie et al., 2012). M., Cerchia, R., Kahn, E., et al. Further studies are required to determine the reason for the difference in
particle size response in animals compared to humans.Although passive targeting, through modifying particle size, enables prolonged retention and improved permeability of nanoparticles, there have been contradictory findings with regards to specificity to diseased versus healthy tissue in the colon (Lamprecht et al., 2005a; Wachsmann et al., 2013).
doi: 10.1016/S0169-409X(01)00112-0CrossRef Full Text | Google Scholar Simmonds, N. B., Kende, M. Of the targets identified, integrin specific ligands appear to be the most promising target for M cells due to its specificity. Oral bioavailability enhancement of agomelatine by loading into nanostructured lipid carriers: Peyer's patch targeting
approach. In comparison to the large intestine, the density of the small intestinal microbiota is much lower, which is likely due to the rapid luminal flow, intestinal fluid volume, and the secretion of bactericidal compounds in this part of the GI tract (El Aidy et al., 2015). doi: 10.1080/17425247.2018.1503249PubMed Abstract | CrossRef Full Text |
Google Scholar Mandal, U. Drugs that alter the motility of the GI tract can also have an impact on the effectiveness of oral drug delivery by affecting the time available for disintegration, dissolution, and/or drug absorption (Watts et al., 1992; Brunton et al., 2018). There is also a potential for electrostatic interactions and subsequent binding of
charged nanoparticles with other charge-modifying substances (e.g., soluble mucins and bile acids) during gastrointestinal transit following oral administration (Hua et al., 2015).Colon-Specific Pharmaceutical StrategiesColon-specific pharmaceutical strategies are likely required to improve nanoparticle accumulation, retention, and drug release in
the colon, as well as minimize drug release in the upper GI tract. Opin. 18 (2), 97–110. Biodegradable polymers have been used in the coatings or matrix of the nanoparticles, including poly-lactic acid (PLA), poly(lactic-co-glycolic acid) (PLGA), and chitosan. doi: 10.1002/jps.1143PubMed Abstract | CrossRef Full Text | Google Scholar Hofmann, D.,
Tenzer, S., Bannwarth, M. T., Yan, Y., Sitaraman, S. Chitosan-coated solid lipid nanoparticles enhance the oral absorption of insulin. K., Chatterjee, B., Senjoti, F. With regards to the ideal particle size for targeting capability in the colon, there have been varying results (Hua et al., 2015). doi: 10.1208/s12249-015-0443-5PubMed Abstract | CrossRef
Full Text | Google Scholar Johansson, M. doi: 10.1016/j.jconrel.2012.10.019PubMed Abstract | CrossRef Full Text | Google Scholar Sercombe, L., Veerati, T., Moheimani, F., Wu, S. Depending on the target region in the GI tract, pharmaceutical strategies may need to be incorporated to protect the nanoparticles from premature interaction or
degradation during transit. doi: 10.1002/jps.20802PubMed Abstract | CrossRef Full Text | Google Scholar Zhang, N., Ping, Q. N., St Amand, A. 11, 575–584. A., Young, V. doi: 10.1016/j.ejps.2012.04.002CrossRef Full Text | Google Scholar Hao, S., Wang, Y., Wang, B. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Use
of lectin-functionalized particles for oral immunotherapy. Solid lipid nanoparticles in lymph and plasma after duodenal administration to rats. Although most drugs are minimally absorbed in the stomach, gastric resections and bariatric surgeries can affect gastric emptying and transit time (Titus et al., 2013). (2007). P., Reddy, G. It should be noted
that mucus is continuously secreted by goblet cells along the GI tract and is subsequently shed and cleared from tissues due to the turnover of cells (Homayun et al., 2019). Intestinal M cells: the fallible sentinels? M., Vllasaliu, D., Lord, J., Stolnik, S. doi: 10.1023/A:1018961204325CrossRef Full Text | Google Scholar Rubinstein, A. C., Jewell, D. doi:
10.1016/j.drudis.2016.05.007PubMed Abstract | CrossRef Full Text | Google Scholar Yu, X., Wen, T., Cao, P., Shan, L., Li, L. doi: 10.1016/j.ajps.2016.04.007CrossRef Full Text | Google Scholar Mane, V., Muro, S. The enteric coat protects against gastric acid and avoids the problem of variable gastric emptying. In addition, cellular uptake can be low
due to a lack of specificity of nanoparticles towards M cells (des Rieux et al., 2006; Yu et al., 2016).Studies have focused on determining the physicochemical characteristics of nanoparticles for optimal uptake by M cells. PubMed Abstract | Google Scholar Lamprecht, A., Yamamoto, H., Takeuchi, H., Kawashima, Y. M., Chakraborty, S., Sheikh, I. L.,
Jurjenson, H., Veski, P., Marvola, M. J., Artursson, P. V., Jain, A. 50 (5), 586–597. doi: 10.1016/S1091-255X(98)80010-3CrossRef Full Text | Google Scholar Timmermans, J., Moes, A. doi: 10.1016/j.drudis.2018.11.009PubMed Abstract | CrossRef Full Text | Google Scholar Hebden, J. E., Path, F. Gastroretentive dosage forms: overview and special case of
Helicobacter pylori. H., Meulbroek, J. Colon Rectum. 14 (12), 4209–4219. J., Cao, Z. (1990). doi: 10.1016/S0378-5173(00)00472-5PubMed Abstract | CrossRef Full Text | Google Scholar Scheline, R. Even within healthy individuals, there is variability in the physiology of the GI tract (Figure 1). The stomach also acts as a temporary reservoir for ingested
food before it is delivered to the duodenum at a controlled rate. In vitro and in vivo evaluation of WGA-carbopol modified liposomes as carriers for oral peptide delivery. doi: 10.1023/A:1011975120776CrossRef Full Text | Google Scholar Beloqui, A., Coco, R., Alhouayek, M., Solinis, M. In rodents, the stomach is divided into the forestomach where
ingested material is stored, and the glandular stomach where digestion continues (Gartner, 2002). Microencapsul. Other considerations include availability of materials and industrial equipment, insufficient batch-to-batch reproducibility to set specifications, and overall cost of dosage form development (Hua et al., 2018). doi:
10.1016/j.jconrel.2005.02.011PubMed Abstract | CrossRef Full Text | Google Scholar Laroui, H., Dalmasso, G., Nguyen, H. 17 (5), 1131–1140. G., et al. The adherent gastrointestinal mucus gel layer: thickness and physical state in vivo. doi: 10.1023/A:1011032328064CrossRef Full Text | Google Scholar Lamprecht, A., Ubrich, N., Yamamoto, H.,
Schafer, U., Takeuchi, H., Maincent, P., et al. doi: 10.1016/j.ijpharm.2012.07.017PubMed Abstract | CrossRef Full Text | Google Scholar Collnot, E. 2 (2), 174–185. doi: 10.1016/j.jconrel.2010.10.002PubMed Abstract | CrossRef Full Text | Google Scholar Kriegel, C., Amiji, M. S., Yuen, K. Advances in the transepithelial transport of nanoparticles.
Therefore, co-administration of other drugs may cause inter-individual and intra-individual variability with respect to oral drug delivery and should be considered in oral formulation design, especially for specific disease indications.Impact of Gastrointestinal Surgery on Oral Drug DeliverySurgical resections of the stomach, small intestine or large
intestine can significantly affect gastrointestinal anatomy and physiology, as well as the effectiveness of oral dosage forms and drug absorption (Titus et al., 2013; Hua et al., 2015; Hatton et al., 2018). doi: 10.1016/j.jconrel.2007.10.023CrossRef Full Text | Google Scholar Thompson, J. Budesonide-loaded nanostructured lipid carriers reduce
inflammation in murine DSS-induced colitis. doi: 10.1021/acsami.7b11821CrossRef Full Text | Google Scholar Lih-Brody, L., Powell, S. A pH-sensitive microsphere system for the colon delivery of tacrolimus containing nanoparticles. Colon: a gateway for chronotherapeutic drug delivery systems. doi: 10.1080/003655201753265082CrossRef Full Text |
Google Scholar Liu, L., Fishman, M. G., Kumar, D., Rampton, D. doi: 10.1039/C7BM01096FPubMed Abstract | CrossRef Full Text | Google Scholar Edsbacker, S., Andersson, T. A., Rasmussen, S. 24 (11), 983–e538. doi: 10.1016/j.jconrel.2006.08.013PubMed Abstract | CrossRef Full Text | Google Scholar Desai, M. The main functions of the GI tract are
the digestion of food, absorption of nutrients, and excretion of waste products (Marieb and Hoehn, 2010; Reinus and Simon, 2014). Physiol. Anti-infect. L., Hicks, K. The mouth and esophagus do not have a distinct mucus layer, but they are washed by mucus from the salivary glands (Johansson et al., 2013). Small intestinal transit time and
intraluminal pH in ileocecal resected patients with Crohn's disease. R., Patel, J. A., Singh, A. Innovative pharmaceutical approaches are also being explored to improve regional drug targeting in the GI tract, with the majority still in the infancy stages of translational development. The mucus is composed of water and mucin protein molecules coated
with proteoglycans, which gives the mucus a negative charge (Homayun et al., 2019). In addition, considerable intra- and inter-individual variability in the pH of the GI tract will affect drug release from pH-dependent dosage forms (Fallingborg et al., 1993; Sasaki et al., 1997; Nugent et al., 2001; Ibekwe et al., 2008; McConnell et al., 2008; Lahner et
al., 2009; Brunton et al., 2018).Mucoadhesive dosage forms, especially intestinal patches, have been investigated to prolong contact with the intestinal mucosa to improve drug absorption (Shen and Mitragotri, 2002; Toorisaka et al., 2012; Banerjee et al., 2016a; Gupta et al., 2016; Banerjee and Mitragotri, 2017). Targeting the intestinal lymphatic
system: a versatile path for enhanced oral bioavailability of drugs. 18 (3), 316–322. Bacteriol. D., et al. doi: 10.3389/fphar.2018.00790PubMed Abstract | CrossRef Full Text | Google Scholar Ibekwe, V. These polymers are generally hydrophilic and are able to hydrate and swell during transit through the GI tract (hence they are also exploited in time-
dependent dosage forms). D., Patel, A. doi: 10.1504/IJBNN.2013.054515CrossRef Full Text | Google Scholar Bhavsar, M. (1998). 42 (6), 620–643. 41 (10), 2078–2086. L., Santi, P., Peppas, N. D., Alonso, M. doi: 10.1111/j.1365-2672.1988.tb02427.xPubMed Abstract | CrossRef Full Text | Google Scholar Mahida, Y. 316 (1-2), 138–143. 12 (11), 3816–
3828. (1999). Efficacy of drug-loaded nanoparticles have been demonstrated in Helicobacter pylori infected animals, even with once daily dosing, due to their mucoadhesive properties (Umamaheshwari et al., 2004; Ramteke et al., 2008; Jain et al., 2009; Ramteke et al., 2009). 11 (12), 4363–4373. S., Quigley, E. However, sheets of nanoparticles and
nanoparticle aggregates were found strongly adhered to the mucosa in the glandular stomach.Most of the in vivo efficacy studies have been focused on using nanoparticulate formulations for treating Helicobacter pylori infection. S., Raut, S. They are able to target diseased tissue of the colon by taking advantage of the abnormally high levels of ROS
that are produced at the sites of inflammation to trigger drug release. Preclinical studies should be conducted under appropriate blinding and randomization to reduce bias. F., Schild, H., et al. Nanosci. Colloid Interface Sci. doi: 10.1152/ajpgi.2001.280.5.G922PubMed Abstract | CrossRef Full Text | Google Scholar Awasthi, R., Kulkarni, G. However,
very few of them have translated to the clinical phase, which is likely due to a combination of biological and pharmaceutical factors. 36 (234), 29–40. J., Wang, G. Ther. M., Durrer, C., Duchene, D., Ponchel, G. 16 (5), 351–380. 24 (3-4), 252–259. E., Zema, L. For example, the success of gastroretentive dosage forms has been limited due to high gastric
motility and rapid mucus turnover. doi: 10.1016/S0378-5173(01)00839-0PubMed Abstract | CrossRef Full Text | Google Scholar Patel, D. Animal Farm: Considerations in Animal Gastrointestinal Physiology and Relevance to Drug Delivery in Humans. Control Release Sep 26122 (2), 141–150. doi: 10.1007/s10620-013-2694-xCrossRef Full Text | Google
Scholar Rao, K. In addition, gastrointestinal transit time can be altered when associated with disease, such as IBD. F., Collnot, E. doi: 10.1038/mt.2013.214PubMed Abstract | CrossRef Full Text | Google Scholar Laroui, H., Viennois, E., Xiao, B., Canup, B. D. Factors controlling the buoyancy and gastric retention capabilities of floating matrix capsules:
new data for reconsidering the controversy. 22 (1), 69–80. R., Chougule, M. 87, 215–221. doi: 10.1111/j.1365-2982.2008.01142.xPubMed Abstract | CrossRef Full Text | Google Scholar Gupta, V., Hwang, B. In general, cationic nanoparticles showed enhanced uptake and transport by enterocytes compared to those with an anionic or neutral charge
(Bannunah et al., 2014; Hellmund et al., 2015; Du et al., 2018) as well as significantly increased oral bioavailability in vivo (Du et al., 2018). Significant pharmaceutical advances have been made to improve the regional targeting of drugs in the GI tract, however very few of them have translated to the clinical phase. In addition, administration of
antibiotics can cause dysbiosis (Sartor, 2010; Albenberg and Wu, 2014) and negatively affect biodegradable dosage forms that rely on enzymes of the microbiome for drug release. Considerations should also be given to the "final product" for clinical use. Natural polysaccharides as targeting tools of drugs to the human colon. For example, cationic
systems are generally considered mucoadhesive, as they adhere to the mucosal surface within inflamed tissue due to the interaction between the negatively charged intestinal mucosa and the positively charged carrier (Liu et al., 2005; Thirawong et al., 2008; Han et al., 2012; Niebel et al., 2012; Coco et al., 2013; Lautenschlager et al., 2013). Control
Release 73 (1), 103–110. Enhanced paracellular transport of insulin can be achieved via transient induction of myosin light chain phosphorylation. By using modified formulations, it is possible to improve targeting to three different parts of the GI tract — namely the stomach, the small intestine, and the colon.Gastroretentive Drug Delivery
SystemsProlonging the gastric residence time of dosage forms is particularly beneficial for drugs that are predominantly absorbed in the stomach or upper GI tract, or for drugs that suffer from solubility issues in the intestinal fluid (Mandal et al., 2016). Expert Opin. J., Ha, D. Hydrogels are dosage forms that provide a platform for protecting
therapeutics through the GI tract and can achieve site-specific delivery by including polymers that exploit fundamental physiological changes (Sharpe et al., 2014). Drug Target Insights 2, 71–81. New advances in the pathophysiology of intestinal ion transport and barrier function in diarrhea and the impact on therapy. Control Release 296, 162–178.
recently recalculated the mucosal surface area of the intestine in humans using morphometric data obtained by light and electron microscopy on biopsies from healthy adult volunteers or patients with endoscopically normal mucosae. For example, pain can alter gastrointestinal physiology by affecting motility, secretion, intestinal permeability,
mucosal blood flow, and the intestinal microbiome (Konturek et al., 2011).Impact of Drugs on Oral Drug DeliveryDrugs can alter the physiology of the GI tract and affect the performance of other co-administered oral dosage forms and the absorption of other drugs. Last but not least, there needs to be a clear benefit of efficacy and/or safety with any
new oral formulation compared to clinically available dosage forms.ConclusionThe oral route of administration is the most preferred route by patients for gastrointestinal drug delivery. Time-controlled oral delivery systems for colon targeting. Systematic adjustment of charge densities and size of polyglycerol amines reduces cytotoxic effects and
enhances cellular uptake. This will ensure stability during transit in the oral cavity and esophagus, as well as maximal release of nanoparticles in the stomach.Nanoparticulate Dosage Forms for Small Intestinal DeliveryNanoparticulate formulations have been applied to the regional targeting of drugs in the small intestine to improve both local and
systemic absorption. W., Sonaje, K., Chung, M. Being mucoadhesive in nature, there is a risk of adhesion with other mucosal surfaces following oral administration before entering the small intestine. doi: 10.1016/j.vaccine.2005.06.031PubMed Abstract | CrossRef Full Text | Google Scholar Marieb, E. This includes cystic fibrosis, Parkinson's disease,
diabetes, HIV infection, and pain (Hatton et al., 2019). Gastrointestinal pH can also affect the ionization state of drug molecules, which in turn influences drug absorption (Brunton et al., 2018).Gastrointestinal MucusThe continuous secretion of mucus in the GI tract is another hurdle for the effective oral delivery of drugs. 204 (1-2), 47–51. ACS Nano
8 (10), 10077–10088. There are two main pathways following uptake into M cells: (i) nanoparticles can be captured by macrophages and dendritic cells in the Peyer's patches, which is beneficial for the development of oral vaccinations (Singh et al., 2015; Yu et al., 2019); and (ii) nanoparticles can undergo passive lymphatic targeting followed by
systemic drug delivery (Cavalli et al., 2003; Joshi et al., 2014; Joshi et al., 2016; Managuli et al., 2018). doi: 10.1016/j.ejps.2014.04.014CrossRef Full Text | Google Scholar Joshi, G., Kumar, A., Sawant, K. Vaccine 23 (48-49), 5599–5617. Bioavailability of nanoparticles in nutrient and nutraceutical delivery. N., Sparrow, R. AAPS PharmSciTech. Control
Release 222, 67–77. There are a number of studies which have reported enhanced systemic absorption of drugs in the small intestine from nanoparticulate formulations (Bargoni et al., 1998; Fonte et al., 2011; Zhang et al., 2011; Reix et al., 2012; Zhang et al., 2013a; Tariq et al., 2016; Ahmad et al., 2018; Prajapati et al., 2018). Modification of the
surface charge of nanoparticles has been investigated to improve mucosal retention and targeting to diseased tissue. B., Messerschmidt, C., Glaser, S. The translational challenges and development aspects of novel formulations will also be addressed.Functional AnatomyThe GI tract is a muscular tube that is approximately 9 meters in length with
varying diameters. Deliv. (1995). Targeting receptors, transporters and site of absorption to improve oral drug delivery. The majority of the intestinal microbiome resides in the anaerobic colon and fermentation of carbohydrates is the main source of nutrition for this population (Macfarlane and Macfarlane, 2011). Pharm. The forestomach of rats and
mice, an effective device supporting digestive metabolism in muridae. BioMed. (1988). 65 (6), 865–879. Biomaterials 26 (29), 5907–5916. 21 (3), 447–453. They showed improved penetration into the space between the intestinal villi, with only low absorption of intact nanoparticles (Li et al., 2017).Improvements in the translocation of nanoparticles
within enterocytes have also been achieved with ligand-mediated active targeting. Gastrointestinal Anatomy and Physiology: The Essentials (UK: John Wiley & Sons). 106 (1), 95–103. Manipulating the formulation can control the dissolution rate and where the drug is released in the GI tract for subsequent absorption. This includes the conjugation of
ligands to the surface of nanoparticles that are specific for the following receptors—vitamin B12 (Chalasani et al., 2007), folate (Anderson et al., 2001; Ling et al., 2009; Jain et al., 2012), biotin (Zhang et al., 2014b), and lectins (Zhang et al., 2005; Yin et al., 2006; Zhang et al., 2006b; Makhlof et al., 2011b). 5 (6), 681–692. A., Jepson, M. 19 (4), 391–
395. Pharmacol. doi: 10.1002/jps.2600840816PubMed Abstract | CrossRef Full Text | Google Scholar Colombo, P., Bettini, R., Santi, P., Peppas, N. PubMed Abstract | Google Scholar Schmidt, T., Pfeiffer, A., Hackelsberger, N., Widmer, R., Meisel, C., Kaess, H. doi: 10.1073/pnas.0706625104CrossRef Full Text | Google Scholar Frey, A., Giannasca, K.
Increased intraluminal release of eosinophil granule proteins EPO, ECP, EPX, and cytokines in ulcerative colitis and proctitis in segmental perfusion. F., Kedziora, K., O'Reilly, M., Maguire, J., Keogh, B., Windle, H., et al. doi: 10.1016/j.jconrel.2004.02.023PubMed Abstract | CrossRef Full Text | Google Scholar Gracie, D. Therefore, transit time may not
be a reliable approach for targeted drug delivery in the colon when associated with some diseases.Biodegradable Dosage FormsThe consistently high levels of resident bacteria in the colon have been exploited for colon-specific drug delivery and is considered a much more reliable factor (McConnell et al., 2008). Overcoming therapeutic obstacles in
inflammatory bowel diseases: a comprehensive review on novel drug delivery strategies. 38 (11), 1989–1993. G., Dyson, T. Delivery of Exenatide and Insulin Using Mucoadhesive Intestinal Devices. Nanoparticles can either be delivered as an oral liquid suspension or loaded into solid-dosage forms (e.g., capsules). 20 (1), 15. C., Melia, C. This
endogenous microenvironment is thought to play a pivotal role in metabolic regulation (El Aidy et al., 2015). Differential Adhesion of Normal and Inflamed Rat Colonic Mucosa by Charged Liposomes. Resection can also significantly change the physiology of the intestinal tract by altering pH, digestion, transit, and nutrient absorption (Spiller et al.,
1988; Schmidt et al., 1996; Fallingborg et al., 1998). Gastrointestinal Surg. Lectin-Conjugated Clarithromycin and Acetohydroxamic Acid-Loaded PLGA Nanoparticles: a Novel Approach for Effective Treatment of H. M., Jani, R. Interestingly, Helander et al. (2013a). B., Madla, C. For more advanced disease, a colectomy (surgical procedure to remove
all or part of the colon) is required, which will alter the local microenvironment and physiology of the GI tract (Titus et al., 2013). 85 (3 Pt A), 578–586. 12 (3), 223–236. Investigation of lectin-modified insulin liposomes as carriers for oral administration. H., Olivier, E. Interplay between intestinal pH, transit time and feed status on the in vivo
performance of pH responsive ileo-colonic release systems. L., Short, M. Recent Pat. Influence of Particle Geometry on Gastrointestinal Transit and Absorption following Oral Administration. Clarithromycin- and omeprazole-containing gliadin nanoparticles for the treatment of Helicobacter pylori. M., Windbergs, M., Lehr, C. J., Laaksonen, P. M.,
Rabbie, S. 558, 367–379. F., Lienemann, A. For example, many acute gastrointestinal infections can cause temporal impairment in the microbiome (dysbiosis) (Britton and Young, 2014), drive increased intestinal fluid secretion (Patel and McCormick, 2014), and may increase or decrease bowel motility (Grover et al., 2008; Albenberg and Wu, 2014).
This coat dissolves on entering the small intestine, revealing a hydrogel plug that then starts to swell. Gastroenterology 103 (1), 186–196. It should be noted that a balance between hydrophilic and hydrophobic properties of the polysaccharides is required. F., Albrecht, R. Table 2 shows some examples of pH-dependent polymer coatings that have
been used for the purpose of colonic targeting either alone or in combination, including some methacrylic resins (commercially available as Eudragit®) (Khan et al., 1999; Goto et al., 2004; Thakral et al., 2013) and hydroxypropyl methylcellulose (HPMC) derivatives (Nykanen et al., 2001; Gareb et al., 2016). doi: 10.1016/j.copbio.2014.09.005PubMed
Abstract | CrossRef Full Text | Google Scholar Eldridge, J. However, the surface area of the large intestinal epithelium is amplified by being arranged into crypt structures. 13 (3-4), 185–223. (2016a). An optimized gastroretentive nanosystem for the delivery of levodopa. M cells are specialized epithelial cells of the gut-associated lymphoid tissues
(GALT) that have a sentinel role for the intestinal immune system by transporting luminal antigens through the follicle-associated epithelium to the underlying immune cells (Miller et al., 2007). doi: 10.1016/j.addr.2016.04.014CrossRef Full Text | Google Scholar Bergin, I. Additional confounders affecting gastrointestinal transit time include the time
of dosing in relation to an individual's bowel movements (Sathyan et al., 2000) and gender, with females having significantly longer colonic transit times (Buhmann et al., 2007).Gastrointestinal pHWith regards to the gastrointestinal environment, differences in pH along the GI tract have been exploited for the purposes of delayed release therapies
(Figure 1). doi: 10.1021/mp400685vPubMed Abstract | CrossRef Full Text | Google Scholar Zhang, X., Qi, J., Lu, Y., He, W., Li, X., Wu, W. 17 (2), 160–167. Digestive Dis. doi: 10.1002/jps.20912PubMed Abstract | CrossRef Full Text | Google Scholar Moss, D. S., Wilding, I. Current applications of polysaccharides in colon targeting. W. Br. J. The M-cell-
mediated pathway has been exploited for nanoparticle drug delivery, as M cells have the advantages of reduced intracellular enzymatic activity as well as a considerably thinner mucus layer and glycocalyx in comparison to enterocytes (Frey et al., 1996; Kyd and Cripps, 2008). B., Tomita, T., Yoshitomi, T., Matsui, H., Nagasaki, Y. 12 (2), 84–92. 5 (2),
e32. Colon-specific drug delivery: new approaches and in vitro/in vivo evaluation. Nanoparticles can then potentially undergo indirect transport to the systemic circulation via the hepatic portal system or direct transport to the systemic circulation via the intestinal lymphatic system. A new method for the quantification of neutrophil and eosinophil
cationic proteins in feces: establishment of normal levels and clinical application in patients with inflammatory bowel disease. Effect of surface chemistry on nanoparticle interaction with gastrointestinal mucus and distribution in the gastrointestinal tract following oral and rectal administration in the mouse. (2016). doi:
10.1517/17425247.2015.1060217CrossRef Full Text | Google Scholar Pawar, V. Gastroenterology 143 (4), 1027–36 e3. G., Spiller, R. Nanoparticles with surface antibody against CD98 and carrying CD98 small interfering RNA reduce colitis in mice. T., Macfarlane, S. 8th ed. doi: 10.1002/btm2.10015CrossRef Full Text | Google Scholar Banerjee, A.,
Qi, J., Gogoi, R., Wong, J., Mitragotri, S. Following uptake into enterocytes and subsequent basolateral secretion into the interstitial space, nanoparticle size can potentially influence whether they are selectively taken up by the lymphatic system or hepatic portal system, with larger particles having a preference for the lymphatic system (Griffin et al.,
2016). Google Scholar Anderson, K. In addition, the composition of the microbiome in the small intestine can significantly fluctuate over a short period of time (e.g., within a day to several days) and is influenced by variations in dietary intake (Booijink et al., 2010). Increased fluid secretion and decreased reabsorption can dilute digestive enzymes and
alter the intestinal microbiome. S., Geem, D., Denning, T. doi: 10.3109/10717544.2014.936535PubMed Abstract | CrossRef Full Text | Google Scholar Banerjee, A., Lee, J., Mitragotri, S. Polyelectrolyte coated multilayered liposomes (nanocapsules) for the treatment of Helicobacter pylori infection. (2008). doi: 10.1016/0016-5085(92)91112-HPubMed
Abstract | CrossRef Full Text | Google Scholar Singh, B., Maharjan, S., Jiang, T., Kang, S. Control Release 150 (1), 77–86. The latter approach has been investigated in a number of studies, whereby nanoparticles are modified with components that are sensitive to pH, enzymes, reactive oxygen species (ROS), and overexpressed receptors (Hua et al.,
2015). 61 (4), 445–449. Mannosylated bioreducible nanoparticle-mediated macrophage-specific TNF-alpha RNA interference for IBD therapy. A., Hirst, B. 9th ed. J., Cho, C. 11 (5), 1520–1532. Clin. The role of PEG on the stability in digestive fluids and in vivo fate of PEG-PLA nanoparticles following oral administration. I. Advances and Challenges of
Liposome Assisted Drug Delivery. doi: 10.1016/j.ijpharm.2014.07.009PubMed Abstract | CrossRef Full Text | Google Scholar Beloqui, A., des Rieux, A., Preat, V. Leukocyte Biol. Gastrointestinal uptake of biodegradable microparticles: effect of particle size. Their design is based on exploiting physiological conditions in the GI tract. 46 (5), 500–507.
Formulation and evaluation of a folic acid receptor-targeted oral vancomycin liposomal dosage form. New directions in the assessment of gastric function: clinical applications of physiologic measurements. doi: 10.1016/j.jconrel.2014.10.026PubMed Abstract | CrossRef Full Text | Google Scholar Makhlof, A., Tozuka, Y., Takeuchi, H. 77 (2), 216–224.
(1996). Vaccine 20 (1-2), 208–217. Gastrointest Liver Physiol. doi: 10.1016/j.ejps.2010.12.007CrossRef Full Text | Google Scholar Makhlof, A., Fujimoto, S., Tozuka, Y., Takeuchi, H. Control Release 116 (3), 337–345. doi: 10.1021/mp5000339PubMed Abstract | CrossRef Full Text | Google Scholar Harel, E., Rubinstein, A., Nissan, A., Khazanov, E.,
Nadler Milbauer, M., Barenholz, Y., et al. 56 (7), 2146–2151. For effective clinical translation, it is likely that the nanoparticles will also need to be loaded into a capsule that is able to dissolve rapidly in the stomach. G., Troost, F. Controlled Release 125 (3), 236–245. These factors are currently lacking in many published studies, which makes it
difficult to assess clinical translatability of the results. Chem. Importantly, the cationic nanoparticles were not only internalized by the intestinal epithelial cells, but they were also transported through these cells into the lamina propria (Du et al., 2018). However, extrapolation of these results to animals and humans is difficult, as there are a number of
significant physiological and pathophysiological factors that affect gastric drug delivery. Gastroenterology 146 (5), 1289–300 e1-19. M., Karlsson, H., Sjovall, H., Hansson, G. doi: 10.1136/gut.38.6.859PubMed Abstract | CrossRef Full Text | Google Scholar Schmidt, C., Lautenschlaeger, C., Collnot, E. doi: 10.1080/10611860802295839CrossRef Full
Text | Google Scholar Ramteke, S., Ganesh, N., Bhattacharya, S., Jain, N. Gastroenterol. Pharmaceutics 11 (3), 129. 6 (2), 593–603. J., Schneider, Y. 35 (4), 327–343. pH-sensitive nanoparticles for colonic delivery of curcumin in inflammatory bowel disease. The small intestine is also the major site of drug absorption, due to its large surface area.
Ansel"s pharmaceutical dosage forms and drug delivery systems. Incorporation of charged polymers has been investigated as a means to reversibly open tight junctions and improve drug delivery across the intestinal epithelial barrier. They might also be unpleasant in taste, cause gastric irritation, and/or undergo first-pass drug elimination processes
in both the intestine and liver (Martinez and Amidon, 2002; Homayun et al., 2019). doi: 10.1021/acs.biomac.6b00685PubMed Abstract | CrossRef Full Text | Google Scholar des Rieux, A., Ragnarsson, E. Goodman & Gilman"s: The Pharmacological Basis of Therapeutics. Hydration of the polymer when in contact with aqueous fluids changes the
structure of the polymer to form a gel layer, which controls the drug release rate (Caraballo, 2010). Gastroenterology 146 (6), 1564–1572. Partial gastric resection or bypass is performed for the treatment of peptic ulcer disease, malignancy, and as a means of weight loss. Biomaterials 34 (30), 7471–7482. Sinking-magnetic microparticles prepared by
the electrospray method for enhanced gastric antimicrobial delivery. The dosage form contains ethyl cellulose-based granules that are approximately 1 mm in size and contain budesonide (corticosteroid). A., Woodward, O. 84 (8), 991–997. Together, these barriers help to prevent pathogens and potential toxins in the gastrointestinal content from
entering the body.Although intestinal barriers play a protective role in the body, they can also restrict the uptake of nanoparticulate formulations by enterocytes, which means that most of the nanoparticles are degraded or eliminated from the body (Yu et al., 2016). Improved localizing method of radiopill in measurement of entire gastrointestinal pH
profiles: colonic luminal pH in normal subjects and patients with Crohn's disease. Surface decorated nanoparticles as surrogate carriers for improved transport and absorption of epirubicin across the gastrointestinal tract: Pharmacokinetic and pharmacodynamic investigations. This typically involves the transport of nanoparticles in endosomes, which
can eventually fuse with the cell membrane for exocytosis or fuse with lysosomes for degradation (Hofmann et al., 2014; Hu et al., 2015). Molecular-phylogenetic characterization of microbial community imbalances in human inflammatory bowel diseases. (1994). Small intestinal bacterial overgrowth and orocecal transit time in patients of
inflammatory bowel disease. Contribution of the microflora to proteolysis in the human large intestine. Fluid-to-matter ratios influence pH and may also affect drug delivery and drug absorption, particularly in the lower GI tract. Pharmacokinet. 3 (11), 1459–1465. C., Brzozowski, T., Konturek, S. In general, the transit time in the small intestine is
considered relatively constant at around 3 to 4 h (Hu et al., 2000). U. Pharmaceut. J., Hardcastle, J. Colonic mucins have a negative charge since their carbohydrates are substituted with a number of sialic acid and sulfate residues (Larsson et al., 2009; Antoni et al., 2014). C., Wilson, C. M., et al. A., Royse, E. Increased oxidative stress and decreased
antioxidant defenses in mucosa of inflammatory bowel disease. S., Udupa, N., Mutalik, S. 104 (9), 2747–2776. 444 (1-2), 162–168. 62 (6), 591–599. It is the most preferred route by patients, due to its advantages, such as ease of use, non-invasiveness, and convenience for self-administration (Shreya et al., 2018; Homayun et al., 2019). There are
several challenges with this particular pathway, including the following: (i) the thick mucus layer overlaying the enterocytes; (ii) the thick glycocalyx coating the surface of the enterocytes; (iii) the luminal enzymes; and (iv) the enzymes in the microvilli of the brush border membrane and within the glycocalyx (Kyd and Cripps, 2008; Lundquist and
Artursson, 2016; Yu et al., 2016). This includes altering luminal pH and transit times, impairing regulation of the ileal brake that controls food transit, and reduction of small chain fatty acid digestion (Kvietys, 1999; Titus et al., 2013; Hua et al., 2015).Similarly, profound changes in gastrointestinal physiology and drug delivery can occur when specific
segments of the GI tract are resected. doi: 10.1016/j.ijpharm.2006.01.032PubMed Abstract | CrossRef Full Text | Google Scholar Miller, H., Zhang, J., Kuolee, R., Patel, G. Size is an important parameter for gastroretentive dosage forms, with particles less than 7 mm in diameter being efficiently evacuated (Timmermans and Moes, 1993; Bardonnet et
al., 2006). H., Macfarlane, G. Both surface charge and PEGylation are promising pharmaceutical strategies for mucosal targeting, however it is likely that additional colon-specific pharmaceutical strategies are needed to localize the nanoparticles in the colon following oral administration and to further improve targeting to diseased tissue (Hua et al.,
2015). J., Barrow, L., Steed, K. This includes understanding the effect of physiology and/or pathophysiology on the distribution, retention, disintegration, and release of drugs from oral dosage forms in the GI tract, as well as correlation with in vivo behavior (e.g., efficacy and safety) in animals and humans. R., Morris, K. For example, the use of
multiparticulate dosage systems, such as nanoparticles, has shown promising results in improving gastrointestinal drug delivery compared to single-unit dose formulations. doi: 10.1371/journal.pone.0024202PubMed Abstract | CrossRef Full Text | Google Scholar Hatton, G. The control and consequences of bacterial fermentation in the human colon.
L., Feldman, R. The hydrophilic surface has also been shown to accelerated drug delivery into the leaky inflamed intestinal epithelium (Lautenschlager et al., 2013). Gastrointestinal physiology is complex and can display both large intra- and inter-individual variability. doi: 10.1016/j.jconrel.2008.05.022CrossRef Full Text | Google Scholar McKeage, K.,
Goa, K. doi: 10.1007/s11095-008-9580-9CrossRef Full Text | Google Scholar Irache, J. 8 (3), 360–364. H., Helariutta, A. Galactosylated trimethyl chitosan-cysteine nanoparticles loaded with Map4k4 siRNA for targeting activated macrophages. Translocation of nanoparticles can also occur by paracellular transport and persorption through gaps or holes
at the villous tips (Hillyer and Albrecht, 2001; des Rieux et al., 2005).Nanoparticulate Dosage Forms for Gastric DeliveryThere are limited studies that have investigated the use of nanoparticulate formulations for gastric drug delivery. In particular, polysaccharide-based systems have shown promising results, with non-starch polysaccharides being
commonly used (Hovgaard and Brondsted, 1996; Rubinstein, 2000; Shah et al., 2011). J., Piffaretti, J. Mass spectrometry and imaging analysis of nanoparticle-containing vesicles provide a mechanistic insight into cellular trafficking. A., Jacobsen, B. F., et al. The advantages and limitations of each pathway are summarized in Table 3.The passage of
nanoparticles by paracellular transport is restricted by the narrow tight junction space, which can range from 0.3 nm to 20 nm, depending on the state (Madara, 1998; Camenisch et al., 1998; Acosta, 2009; Chen et al., 2013). J., Allen, R. doi: 10.1136/gut.30.10.1362PubMed Abstract | CrossRef Full Text | Google Scholar Maisel, K., Ensign, L., Reddy,
M., Cone, R., Hanes, J. Control Release 165 (2), 139–145. W., Kim, H. J. J., Wang, J. F., Basit, A. 42, 1–20. Manipulation Of drug release using Eudragit L100-55 and Eudragit S100 combinations. Targeting the colon with such polymers has proved difficult due to considerable intra- and inter-individual variability in the pH of the GI tract (McConnell et
al., 2008), which is also influenced by diet (Ibekwe et al., 2008), disease (Fallingborg et al., 1993; Sasaki et al., 1997; Nugent et al., 2001), and co-administered drugs (Lahner et al., 2009; Brunton et al., 2018). doi: 10.2165/00003495-200262150-00015PubMed Abstract | CrossRef Full Text | Google Scholar Meissner, Y., Pellequer, Y., Lamprecht, A. 17
(5), 607–613. Pharmaceutics 11 (4), 193. A pH-dependent colon targeted oral drug delivery system using methacrylic acid copolymers. L., Liao, Z. doi: 10.1016/j.addr.2012.10.010CrossRef Full Text | Google Scholar Chionh, Y. J., Davis, S. Entrapment and degradation of nanoparticles within lysosomes prevent exocytosis at the basolateral membrane,
which affects the efficacy of nanoparticulate formulations (Yu et al., 2016; Reinholz et al., 2018).Several approaches have been utilized to improve the delivery and transcytosis of nanoparticles across enterocytes in the small intestine. doi: 10.1016/j.addr.2016.07.007CrossRef Full Text | Google Scholar Macfarlane, G. P., Bimbo, L. doi:
10.1016/j.ijpharm.2016.01.054PubMed Abstract | CrossRef Full Text | Google Scholar Taverner, A., Dondi, R., Almansour, K., Laurent, F., Owens, S. doi: 10.1021/acs.molpharmaceut.5b00265PubMed Abstract | CrossRef Full Text | Google Scholar Singodia, D., Verma, A., Verma, R. A complex, but uniform O-glycosylation of the human MUC2 mucin
from colonic biopsies analyzed by nanoLC/MSn. Glycobiology 19 (7), 756–766. Efficient mucus permeation and tight junction opening by dissociable "mucus-inert" agent coated trimethyl chitosan nanoparticles for oral insulin delivery. W., Merchant, H. C., Kosterink, J. 14 (3), 1012–1024. 437 (1-2), 213–220. H., Summers, R. Numerous enzymes are
produced by the colonic bacterial flora, such as polysaccharidases, azoreductases, and glycosidases (Scheline, 1973; Cummings and Macfarlane, 1991; Rubinstein, 2000), and have been utilized in drug delivery approaches. However, the performance of the dosage forms and drug absorption are highly dependent on the physiology of the GI tract. doi:
10.1053/j.gastro.2014.01.059PubMed Abstract | CrossRef Full Text | Google Scholar Brunton, L. 17 (3), 669–674. doi: 10.1023/A:1007561129221CrossRef Full Text | Google Scholar Hu, Y. PubMed Abstract | Google Scholar Sathyan, G., Hwang, S., Gupta, S. A., et al. In some cases, the entire colon can also be affected (pancolitis). (2018). Interf. For
example, biodegradable polymers in coatings and/or matrix formulations have been used for regional drug targeting in the colon. Nano Today 16, 82–96. doi: 10.1023/A:1015806211556CrossRef Full Text | Google Scholar Wilson, D. Very low intraluminal colonic pH in patients with active ulcerative colitis. Biomatter 1 (1), 57–65. (2011a). Am. J. doi:
10.1016/S0264-410X(01)00258-4PubMed Abstract | CrossRef Full Text | Google Scholar Coco, R., Plapied, L., Pourcelle, V., Jerome, C., Brayden, D. Understanding the relationship between biology and pharmaceutics are important determinants for the successful translation of new formulations (Hua et al., 2018). doi:
10.1016/j.nano.2011.07.002PubMed Abstract | CrossRef Full Text | Google Scholar Spiller, R. Gastroenterology 138 (3), 843–53 e1-2. 92 (1), 114–118. For example, there has been limited studies focused on the toxicology of nanoparticles in the GI tract of humans — this is likely to vary according to the size and composition of the particles (Bergin and
Witzmann, 2013; Talkar et al., 2018; Vita et al., 2019). C., Metselaar, J. For example, vagotomy can delay gastric emptying, whereas resection of the pylorus can accelerate gastric emptying (Titus et al., 2013).Intestinal resections can be the result of a number of diseases, including in severe IBD, malignancy, and in intestinal malrotation with
ischemia. Evaluation of Pulsincap to provide regional delivery of dofetilide to the human GI tract. W., Frijlink, H. Nanoparticulate Drug Delivery Systems Targeting Inflammation for Treatment of Inflammatory Bowel Disease. A., Boedeker, E. doi: 10.1517/17425247.2012.730517PubMed Abstract | CrossRef Full Text | Google Scholar Xiao, B., Laroui,
H., Ayyadurai, S., Viennois, E., Charania, M. K., Shewale, N. A., Staas, J. Anatomically, it can be further divided into four parts — ascending, transverse, descending, and sigmoid colon. V., Sharma, S., Malik, A., Kaur, J., Prasad, K. Studies have demonstrated an inverse correlation between particle size and cellular uptake, with improved uptake with
smaller nanoparticles (50 nm > 200 nm > 500 nm > 1000 nm) (Desai et al., 1996; Bannunah et al., 2014; Banerjee et al., 2016b). (1997). It would also be important to understand the performance of nanoparticulate dosage forms under both fed and fasted conditions. Adv. K. K., Tice, T. doi: 10.1136/gut.48.4.571PubMed Abstract | CrossRef Full Text |
Google Scholar Nykanen, P., Lempaa, S., Aaltonen, M. (2013b). View PDFVolume 170, 1 March 2022, 106098 rights and contentIn silico models, oral biopharmaceutics The oral route is by far the most common route for drug administration in the gastrointestinal tract (GI tract) and can be used for both systemic drug delivery and for treating local
gastrointestinal diseases. 13 (T-NANO 2014 Abstracts), 35–38. Timing of drug release is governed by the amount of hydrogel, in that the hydrogel plug is ejected from the bottom half of the capsule with extensive swelling.In addition, Entocort® EC is another example of a dosage form that uses a combination of pH and gastrointestinal transit time
(McKeage and Goa, 2002; Edsbacker and Andersson, 2004). Although there are very few studies available, the initial in vivo results have demonstrated localization and efficacy of these nanoparticles to sites of intestinal inflammation in mice with colitis following oral administration (Wilson et al., 2010).Ligand-mediated active targeting is another
promising strategy to enhance drug accumulation and uptake to sites of disease within the colon. N., Amidon, G. K., Evans, D. For example, the fluid environment permits contact of digestive enzymes with food particles, assists in the transit of intestinal contents along the length of the GI tract without damage to the epithelial lining, and supports the
dissolution and absorption of nutrients and drugs (Reinus and Simon, 2014). This can affect carbohydrate and polysaccharide digestion (Yang, 2008) as well as contribute to changes in intestinal transit times (Van Citters and Lin, 2006). Nanorods also exhibited significantly longer retention time in the GI tract (especially in the jejunum and ileum)
compared to nanospheres, which allowed more time for intestinal absorption (Li et al., 2017). doi: 10.1016/S0378-5173(02)00012-1PubMed Abstract | CrossRef Full Text | Google Scholar Streubel, A., Siepmann, J., Bodmeier, R. Investigation of the influence of particle size on the excipient percolation thresholds of HPMC hydrophilic matrix tablets.
doi: 10.1016/j.ejpb.2016.03.018PubMed Abstract | CrossRef Full Text | Google Scholar Gartner, G. doi: 10.1177/117739280700200003PubMed Abstract | CrossRef Full Text | Google Scholar Han, H. 9, 790. Ideally, gastroretentive dosage forms should remain in the stomach for a specific duration and be able to undergo clearance from the body.
[Adapted from (Hua et al., 2015)].Gastrointestinal transit time is an important factor for dosage forms and drugs that have region-specific targeting or absorption properties (Figure 1). They are typically composed of hydrophilic polymers (e.g., ethyl cellulose and HPMC) in the coating or matrix that are able to gradually swell over time, which creates
a lag phase before releasing the drug (Sangalli et al., 2001; Gazzaniga et al., 2006; Gareb et al., 2016). 251, 191–202. The inflammation is continuous in UC and is confined to the colon (Podolsky, 2002). Screening of surface markers on rat intestinal mucosa microfold cells by using laser capture microdissection combined with protein chip technology.
Environ. C., Choonara, Y. doi: 10.1007/s10439-016-1558-xCrossRef Full Text | Google Scholar Hamman, J. doi: 10.1016/j.jconrel.2007.03.006PubMed Abstract | CrossRef Full Text | Google Scholar Booijink, C. E., Perkins, A. Nanomedicine 11 (5), 1117–1132. In addition, non-ionic nanoparticles composed of hydrophobic constituents have better uptake
by M cells in comparison to hydrophilic and charged nanoparticles (Bargoni et al., 1998; Shakweh et al., 2004; Managuli et al., 2018).Active targeting strategies have also been applied to improve specificity of targeting to M cells. Drug absorption in the GI tract is governed by many factors such as surface area for absorption, blood flow to the site of
absorption, the physical state of the drug (such as a solution, suspension or solid dosage form), its water solubility, and the concentration of the drug at the site of absorption (Martinez and Amidon, 2002; Brunton et al., 2018). Biomacromolecules 17 (7), 2479–2488. This includes the conjugation of ligands to the surface of nanoparticles that are
specific for the following — macrophage receptors (e.g., mannose receptors and macrophage galactose-type lectin) (Coco et al., 2013; Xiao et al., 2013; Zhang et al., 2013b; Laroui et al., 2014b), intercellular adhesion molecule-1 (ICAM-1) (Mane and Muro, 2012), transferrin receptors (Harel et al., 2011), and glycoprotein CD98 (Xiao et al., 2014). 18
(6), 788–793. Although this parameter was not assessed in other in vivo studies on nanoparticles, those on microparticulate dosage forms have shown prolonged gastric retention of over 8 h in the fasted state (Hao et al., 2014). An enteric coating is defined as a material, usually a polymer, that forms a barrier over the surface of the dosage form that
permits transit through the stomach to the small intestine before the drug is released (Felton and Porter, 2013; Thakral et al., 2013). doi: 10.1016/j.addr.2016.06.006CrossRef Full Text | Google Scholar Grover, M., Kanazawa, M., Palsson, O. 327 (1-2), 153–159. doi: 10.1016/S0168-3659(97)00266-6PubMed Abstract | CrossRef Full Text | Google
Scholar Wilding, I. doi: 10.1002/jps.10368PubMed Abstract | CrossRef Full Text | Google Scholar Chalasani, K. H., Hammond, C. Google Scholar Buhmann, S., Kirchhoff, C., Ladurner, R., Mussack, T., Reiser, M. doi: 10.1080/10611860902718649CrossRef Full Text | Google Scholar Rana, S. Chemiluminescence assay of mucosal reactive oxygen
metabolites in inflammatory bowel disease. 13 (10), 1477–1486. A mechanistic approach to understanding the factors affecting drug absorption: a review of fundamentals. Budesonide loaded nanoparticles with pH-sensitive coating for improved mucosal targeting in mouse models of inflammatory bowel diseases. Oral colon-specific therapeutic
approaches toward treatment of inflammatory bowel disease. 1 (4), 299–308. The inflammatory response at the mucosa, along with severe diarrhea, will also disrupt the resident microbiome by affecting the composition and diversity of the bacterial species (Linskens et al., 2001). 97 (7), 1755–1762. Control Release 186, 41–53. A., Daily, A. Mechanism
study of cellular uptake and tight junction opening mediated by goblet cell-specific trimethyl chitosan nanoparticles. (1973). 23 (2), 378–394. doi: 10.1007/BF01297074CrossRef Full Text | Google Scholar Fallingborg, J., Pedersen, P., Jacobsen, B. 454 (2), 775–783. 9 (5), 654–657. 70 (6), 443–459. Gut 48 (4), 571–577. doi: 10.1016/S0168-
3659(98)00151-5PubMed Abstract | CrossRef Full Text | Google Scholar Konturek, P. R. Therefore, active inflammation significantly alters the physiology of the GI tract, which can particularly affect the efficacy of conventional oral drug delivery approaches (Hua et al., 2015).Furthermore, there is increasing evidence showing that non-gastrointestinal
systemic diseases can also cause physiological and functional changes in the GI tract that can affect the performance of oral dosage forms and the absorption of drugs. (Philadelphia: Lippincott Williams & Wilkins). For example, food intake can significantly alter free fluid volumes, bile salts, and digestive enzyme levels in the GI tract (Reinus and
Simon, 2014). J., Reggio, H., Lencer, W. doi: 10.1128/AEM.56.7.2146-2151.1990PubMed Abstract | CrossRef Full Text | Google Scholar Ramteke, S., Jain, N. Drug molecules can be transported passively via paracellular diffusion (between cells) and transcellular diffusion (through the cell) or actively via receptor-mediated endocytosis and carrier-
mediated transport. K., Hua, S. Transl. Infect. Pharmacokinetic, pharmacodynamic and biodistribution following oral administration of nanocarriers containing peptide and protein drugs. Asian J. For example, shortening of the intestine can reduce the transit distance through the GI tract, which potentially affects the way conventional oral
formulations are processed (Kvietys, 1999; Titus et al., 2013). doi: 10.1007/s13346-011-0023-5CrossRef Full Text | Google Scholar Foster, N., Clark, M. The decrease in fatty acids reduces the ileal brake, which is a nutrient feedback mechanism that slows transit times to allow nutrient absorption (Van Citters and Lin, 1999; Van Citters and Lin, 2006).
S., Meyer, J. P., Gasco, M. The amount of time needed for a dosage form to leave the stomach is highly variable and can range from several minutes to several hours (Reinus and Simon, 2014). In vitro uptake evaluation in Caco-2 cells and in vivo results in diabetic rats of insulin-loaded PLGA nanoparticles. doi: 10.1016/j.nano.2013.07.011PubMed
Abstract | CrossRef Full Text | Google Scholar Zhang, S., Langer, R., Traverso, G. Engineering 44 (6), 1993–2007. 60, 80–89. Prodrugs essentially rely on the enzymatic activity of colonic bacteria to break down an inactive precursor and release the active drug moiety. (2014a). The biological challenges and pharmacological opportunities of orally
administered nanomedicine delivery. Control Release 160 (3), 659–665. PloS One 6 (9), e24202. doi: 10.1039/c0nr00879fPubMed Abstract | CrossRef Full Text | Google Scholar Zhang, Z., Huang, J., Jiang, S., Liu, Z., Gu, W., Yu, H., et al. doi: 10.1016/j.actbio.2011.09.023PubMed Abstract | CrossRef Full Text | Google Scholar Tripathi, J., Thapa, P.,
Maharjan, R., Jeong, S. Drug Carrier Syst. Sarparanta et al. The combination approach has shown promising results in improving drug release in the colon and reducing premature drug release in the upper GI tract. 10 (6), 352–361. Advances in oral nano-delivery systems for colon targeted drug delivery in inflammatory bowel disease: selective
targeting to diseased versus healthy tissue. doi: 10.1016/0168-3659(94)00033-6CrossRef Full Text | Google Scholar Jain, P., Jain, S., Prasad, K. 236 (1-2), 27–34. K., Choi, Y. doi: 10.1053/j.gastro.2012.06.043PubMed Abstract | CrossRef Full Text | Google Scholar Wachsmann, P., Moulari, B., Beduneau, A., Pellequer, Y., Lamprecht, A. 9 (11), 1393–
1407. Med. 9 (11), 923–928. 43 (4), 702–705. (2017). Vitamin B12 ligand-mediated transport is limited by the relatively slow uptake of vitamin B12 in the GI tract as well as restricted site for absorption in the distal ileum (Hamman et al., 2007; Zhang and Wu, 2014). doi: 10.1016/j.ijpharm.2006.07.026PubMed Abstract | CrossRef Full Text | Google
Scholar Zhang, Z., Huang, Y., Gao, F., Bu, H., Gu, W., Li, Y. Porous starch based self-assembled nano-delivery system improves the oral absorption of lipophilic drug. Pharmaceutical design of a novel colon-targeted delivery system using two-layer-coated tablets of three different pharmaceutical formulations, supported by clinical evidence in humans.
Both genetic and environmental factors contribute to the considerable variation in the composition of the microbiome that is seen between individuals (Sartor, 2010). Gastro-retentive drug delivery systems and their in vivo success: a recent update. ACS Appl. In addition, the viscosity of the mucus-gel layer is affected by intestinal fluid secretion
(Johansson et al., 2013; Reinus and Simon, 2014), which may influence the ability of drugs to be taken up by cells at the site of action. doi: 10.1016/j.ijpharm.2005.01.018PubMed Abstract | CrossRef Full Text | Google Scholar Zhang, N., Ping, Q., Huang, G., Xu, W., Cheng, Y., Han, X. N., Blake, D. For example, conventional delayed release
formulations have been reported to show asymmetric drug distribution in the colon, with significantly lower drug concentrations in the distal colon and higher drug retention in the proximal colon (Hebden et al., 2000). Cooper Medical Research Foundation, Gladys M Brawn Fellowship, and ausEE Research Foundation for providing financial support
for this work.References Acosta, E. doi: 10.1016/j.ejpb.2013.09.016PubMed Abstract | CrossRef Full Text | Google Scholar Li, D., Zhuang, J., He, H., Jiang, S., Banerjee, A., Lu, Y., et al. Complex interactions among diet, gastrointestinal transit, and gut microbiota in humanized mice. Absorption sites of orally administered drugs in the small intestine.
These formulations typically rely on the relatively constant transit time through the small intestine, and work on the assumption that a dosage form will spend approximately 6 h in the stomach and small intestine in the fasted state. doi: 10.1046/j.1365-2036.2000.00697.xCrossRef Full Text | Google Scholar Hellmund, M., Achazi, K., Neumann, F.,
Thota, B. C., Prather, C., Fisher, R. Nanoscale 3 (4), 1780–1787. Of these pathways, the transcellular route is the main mechanism of drug absorption in the GI tract and is usually proportional to the lipid solubility of the drug (Brunton et al., 2018; Homayun et al., 2019). H., Xu, W. B., Raut, S. Azo-reductase activated budesodine prodrugs for colon
targeting. Acta Biomater. doi: 10.1586/eri.12.47PubMed Abstract | CrossRef Full Text | Google Scholar Hovgaard, L., Brondsted, H. doi: 10.1016/j.ejpb.2008.12.013PubMed Abstract | CrossRef Full Text | Google Scholar Makhlof, A., Tozuka, Y., Takeuchi, H. Daily water balance in the healthy adult human GI tract includes secretion from saliva (1.5 L),
gastric juice (2.5 L), pancreatic juice (1.5 L) and other intestinal components (~1 L), as well as absorption from the small intestine (7 L) and large intestine (1.9 L) (Reinus and Simon, 2014). doi: 10.1016/j.biomaterials.2012.01.029PubMed Abstract | CrossRef Full Text | Google Scholar Sartor, R. doi: 10.1016/S0264-410X(97)00222-3PubMed Abstract |
CrossRef Full Text | Google Scholar Frank, D. Enhanced bioavailability and intestinal uptake of Gemcitabine HCl loaded PLGA nanoparticles after oral delivery. (2019). In particular, drug release from hydrophilic matrices depends on several processes, including swelling of the polymer, penetration of water through the matrix, drug dissolution, drug
transport through the swelled polymer, and erosion of the matrix (Colombo et al., 1995; Colombo et al., 2000; Caraballo, 2010). doi: 10.1016/j.jconrel.2006.09.015PubMed Abstract | CrossRef Full Text | Google Scholar Youngren, S. Drug Delivery 11 (9), 1343–1350. V., Popovich, N. 7 (4), 932–939. Biotechnol. M., Ali, H., Lehr, C. doi:
10.1023/B:PHAM.0000019298.29561.cdCrossRef Full Text | Google Scholar Kagan, L., Hoffman, A. (Sarparanta et al., 2012) reported that the majority of the orally administered mucoadhesive nanoparticles were found to be mixed with material that the animals had ingested during the experiment (e.g., hair and bedding chips) in the forestomach.
Attempts to overcome these issues have focused on improved understanding of the physiology of the GI tract in both healthy and diseased states. Biorelevant dissolution testing of colon-specific delivery systems activated by colonic microflora. Fermentation in the human large intestine: its physiologic consequences and the potential contribution of
prebiotics. doi: 10.1016/j.ejpb.2010.12.008PubMed Abstract | CrossRef Full Text | Google Scholar Managuli, R. (2014). Gastroretentive dosage forms: a review with special emphasis on floating drug delivery systems. doi: 10.1016/j.jconrel.2007.05.019CrossRef Full Text | Google Scholar Chen, M. Hepatol. F. As previously discussed for conventional
formulations, biodegradable polymers can suffer from premature drug release or burst release based on their hydrophilicity and solubility in the upper GI tract.Redox-based nanoparticulate formulations have shown promise for enhancing drug accumulation at sites of colonic inflammation (Wilson et al., 2010). Rev. The commonly affected regions
include the terminal ileum and the colon (Podolsky, 2002). (2006). doi: 10.1016/j.jconrel.2014.03.039PubMed Abstract | CrossRef Full Text | Google Scholar Allen, L. In particular, enteric-coated solid dosage forms (e.g., tablets and capsules) are commonly used and are available clinically (Thakral et al., 2013; Al-Gousous et al., 2017). This strategy
involves the conjugation of ligands to the surface of nanoparticles and exploits cell-specific differences or disease-induced changes in the expression of receptors, proteins, and adhesion molecules on the surface of tissues (Hua et al., 2015; Sercombe et al., 2015). 3 (1-2), 1–44. doi: 10.1211/jpp.61.04.0005PubMed Abstract | CrossRef Full Text | Google
Scholar Linskens, R. Dis. Different HPMC viscosity grades as coating agents for an oral time and/or site-controlled delivery system: an investigation into the mechanisms governing drug release. Glycoprotein CD98 as a receptor for colitis-targeted delivery of nanoparticle. Y., Jensen-Jarolim, E., Untersmayr, E., Gabor, F. However, it can still suffer from
the intra- and inter-individual variability that can occur with each of these gastrointestinal parameters.Nanoparticulate Oral Drug Delivery ApproachesThe development of novel gastrointestinal drug delivery systems has gained increasing interest, due to the inconsistent efficacy and inter-patient variability of conventional approaches that mostly rely
on non-stable parameters in the GI tract. Biomaterials 34 (14), 3667–3677. The diameter of the pylorus is approximately 12 ± 7 mm (Timmermans and Moes, 1993), which means that the size of the dosage form needs to be larger. C., Basit, A. Freeze-dried targeted mannosylated selenium-loaded nanoliposomes: development and evaluation. Z., Sutton,
P. Nanoparticulate dosage forms have shown the following advantages for gastrointestinal drug delivery, owing to their smaller size: (i) easier transport through the GI tract; (ii) more uniform distribution and drug release; (iii) increase in residence time of particles in the GI tract, even when colonic motility is increased in diarrhea; (iv) improved
uptake into mucosal tissues and cells; and (v) specific accumulation to the site of disease, such as inflamed tissues (Hua et al., 2015; Moss et al., 2018; Reinholz et al., 2018). S., Mumtaz, S., Scarsbrook, A. F., Pye, G., Bramley, R., Clark, A. M., Selby, W., Harrison, J. For example, drugs used to reduce gastric acid secretion (e.g., proton pump inhibitors
and histamine H2-receptor antagonists) or modify pH (e.g., antacids) (Lahner et al., 2009; Brunton et al., 2018) can affect dosage forms that rely on the difference in pH in various regions of the GI tract to trigger drug release. Oral absorption of peptides and nanoparticles across the human intestine: Opportunities, limitations and studies in human
tissues. Controlled vaccine release in the gut-associated lymphoid tissues. However, the dominant species (Firmicutes, Bacteroidetes, Proteobacteria, Actinobacteria, and Fusobacteria) appear to be consistent and represent the majority of the colonic flora (Frank et al., 2007; Consortium, 2012).Interestingly, the gastrointestinal microbiome not only
resides in the large intestine but is also found in the small intestine. However, some drugs are known to have preferential absorption sites in the small intestine (Murakami, 2017).Regional Delivery of Drugs to the ColonColon targeted drug delivery is an active area of research, particularly for the treatment of local diseases affecting the colon, such as
IBD and colorectal cancer. Streptococcus and Veillonella species are also consistently found in the small intestine. Role of the glycocalyx in regulating access of microparticles to apical plasma membranes of intestinal epithelial cells: implications for microbial attachment and oral vaccine targeting. For example, both pH and time-dependent strategies
are commonly used to improve drug delivery to the colon (Zema et al., 2007; Talaei et al., 2013; Patel, 2015). doi: 10.1016/j.jcis.2019.08.027PubMed Abstract | CrossRef Full Text | Google Scholar Zema, L., Maroni, A., Foppoli, A., Palugan, L., Sangalli, M. doi: 10.1016/j.jconrel.2007.10.026PubMed Abstract | CrossRef Full Text | Google Scholar Yin, Y.,
Chen, D., Qiao, M., Lu, Z., Hu, H. Preparation and characterization of nanocapsules for colon-targeted drug delivery system. Mucus gel thickness and turnover in the gastrointestinal tract of the rat: response to cholinergic stimulus and implication for mucoadhesion. The endosomal-lysosomal system: from acidification and cargo sorting to
neurodegeneration. doi: 10.1016/j.ejps.2005.04.015CrossRef Full Text | Google Scholar des Rieux, A., Fievez, V., Garinot, M., Schneider, Y. Drying technology strategies for colon-targeted oral delivery of biopharmaceuticals. Targeting intestinal inflammation with CD98 siRNA/PEI-loaded nanoparticles. F., Chowdhury, F. N., Mohapatra, S. Assessment
of colonic transit time using MRI: a feasibility study. doi: 10.1016/S0169-409X(00)00070-3CrossRef Full Text | Google Scholar Clark, M. doi: 10.1007/s00330-006-0414-zPubMed Abstract | CrossRef Full Text | Google Scholar Byrne, C. Anionic nanoparticles are able to interdiffuse among the mucus network due to less electrostatic interaction with the
mucus in comparison to cationic nanoparticles, which can suffer from immobilization following binding to the mucus (Hua et al., 2015).Similarly, PEGylated nanoparticles have been demonstrated to improve particle translocation through the mucus as well as mucosa (Tobio et al., 2000; Vong et al., 2012; Lautenschlager et al., 2013). Interaction of
various pectin formulations with porcine colonic tissues. Development of a zero-order sustained-release tablet containing mesalazine and budesonide intended to treat the distal gastrointestinal tract in inflammatory bowel disease. (2001a). Control Release 197, 48–57. R., et al. 103, 32–42. B. Small intestinal bacterial overgrowth in irritable bowel
syndrome: association with colon motility, bowel symptoms, and psychological distress. The size of the nanoparticles may also improve mucosal interaction, with the potential for cellular uptake and/or close interaction for efficient drug delivery. doi: 10.1080/02652048.2018.1485755PubMed Abstract | CrossRef Full Text | Google Scholar Albenberg, L.
J., Smidt, H., et al. Alginate-chitosan coated layered double hydroxide nanocomposites for enhanced oral vaccine delivery. Systematic review: impaired drug absorption related to the co-administration of antisecretory therapy. H., Vandenbroucke-Grauls, C. The high concentration of ROS is typically generated by activated phagocytes (Mahida et al.,

1989). W., Pimentel, M., et al. R., Davis, S. Interactions of mussel-inspired polymeric nanoparticles with gastric mucin: Implications for gastro-retentive drug delivery. 14, 3–15. Drug Dev. V., Jain, S. Various receptors expressed on the surface of enterocytes have demonstrated improved uptake and transcytosis of nanoparticles, with improve systemic bioavailability and therapeutic efficacy of encapsulated therapeutics (Zhang and Wu, 2014; Griffin et al., 2016). L., Witzmann, F. However, this can range from 2 to 6 h in healthy individuals (Reinus and Simon, 2014). Drug Discovery Today 24 (2), 417–427. Biomaterials 29 (34), 4554–4560. Budesonide (Entocort EC Capsules): a review of its therapeutic use in the management of active Crohn's disease in adults. Among these challenges are poor drug solubility, poor drug stability, and low drug permeability across the mucosal barriers (Martinez and Amidon, 2002). Considerations should also be given to physiological heterogeneity in the GI tract of both healthy patients and those with specific pathological conditions (Titus et al., 2013; Hua et al., 2015; Hatton et al., 2018; Hatton et al., 2019).For innovative platforms, such as nanoparticles, safety of the different carriers following uptake needs to be evaluated further. C Mater. C., Marcobal, A., Ursell, L. doi: 10.1208/s12249-018-1262-2PubMed Abstract | CrossRef Full Text | Google Scholar Siepmann, J., Peppas, N. 6, 286. World J. The studies have shown promising results with regard to gastric retention and/or mucoadhesion in both in vitro and ex vivo experiments. In addition, nanoparticles have also been embedded in hydrogel matrices containing polymers that have been shown to be specifically degraded by enzymes in the colon (Laroui et al., 2010; Laroui et al., 2014a; Laroui et al., 2014b; Xiao et al., 2014). C., Chitralekha, K. K., Talegaonkar, S. C., Harpaz, N., Pace, N. Duodenal administration of solid lipid nanoparticles loaded with different percentages of tobramycin. doi: 10.1111/j.1365-2036.2009.03993.xCrossRef Full Text | Google Scholar Lamprecht, A., Schäfer, U., Lehr, C.-M. Anim. Control Release 55 (1), 3–12. G., Bakhshaee, M., Binns, J. It should be noted that there are limited M cell specific targets that have been identified (Zhao et al., 2014), with many also being expressed on other elements in the GI tract. Crohn's inflammation, however, is generally discontinuous in manner and can affect any region of the GI tract. T., Guo, J., Presas, E., Donovan, M. doi: 10.2147/IJN.S124703CrossRef Full Text | Google Scholar Rafii, F., Franklin, W., Cerniglia, C. Biodistribution and endocytosis of ICAM-1-targeting antibodies versus nanocarriers in the gastrointestinal tract in mice. Of these approaches, the floating dosage forms are the most common commercialized gastroretentive drug delivery system (Kumar and Kaushik, 2018). Control Release 104 (2), 337–346. Together these changes can increase colonic epithelial permeability.During relapse of IBD, patients suffering from severe mucosal inflammation may exhibit altered gastrointestinal motility and diarrhea, which in turn affects intestinal volume, pH, and mucosal integrity (Hua et al., 2015). doi: 10.1016/j.coph.2006.04.007PubMed Abstract | CrossRef Full Text | Google Scholar Sunoqrot, S., Hasan, L., Alsadi, A., Hamed, R., Tarawneh, O. doi: 10.1021/mp500439cPubMed Abstract | CrossRef Full Text | Google Scholar Bardonnet, P. Lett. M., Solomon, M. These factors promote easier access and intracellular transport. The effect of the small intestinal microbiota on oral dosage forms and drug absorption has not yet been elucidated.Pathophysiological Factors Influencing Oral Drug DeliveryAdding to this complexity are the changes in gastrointestinal physiology associated with gastrointestinal or systemic disease, concurrent medications, and gastrointestinal surgery. N., Wilson, C. (2001b). Factors affecting drug release from hydroxypropyl methylcellulose matrix systems in the light of classical and percolation theories. (2005a). Control Release 11, 205–214. The remaining waste is then sent to the rectum and discharged from the body as stool. Citric acid as excipient in multiple-unit enteric-coated tablets for targeting drugs on the colon. Transferrin as a luminal target for negatively charged liposomes in the inflamed colonic mucosa. This approach is usually used to improve physicochemical properties of drugs (e.g., solubility, permeability, and stability) and/or to target drug release to a specific site in the GI tract. B., Ren, R. Intestinal patches for oral drug delivery. Combinatorial Approach of Antigen Delivery Using M Cell-Homing Peptide and Mucoadhesive Vehicle to Enhance the Efficacy of Oral Vaccine. Most of the digestion then takes place in the stomach by the action of acid and enzymes, especially peptidases (Reinus and Simon, 2014). Improving the delivery of drugs to the colon not only improves the local effectiveness of therapeutics, but it can also reduce the risk of systemic adverse effects. N., Hoehn, K. Intestinal mucoadhesive devices for oral delivery of insulin. doi: 10.1128/IAI.01522-08PubMed Abstract | CrossRef Full Text | Google Scholar Clark, M. H., Demana, P. Mater. doi: 10.1517/17425247.2014.902047PubMed Abstract | CrossRef Full Text | Google Scholar Shen, Z., Mitragotri, S. B., Yadav, V., Basit, A. K., Das, M., Godugu, C. In addition, the physiological environment in the GI tract can also affect the stability and solubility of drugs (Martinez and Amidon, 2002; Shreya et al., 2018; Homayun et al., 2019).There are generally three main goals in formulation design for the oral route of gastrointestinal drug delivery (Martinez and Amidon, 2002): (i) local drug delivery to treat gastrointestinal disease, whereby the drug generally needs to be taken up into gastrointestinal mucosa but will not be systemically absorbed or will be poorly absorbed; (ii) systemic drug delivery, where drug absorption needs to be able to traverse the mucosal wall into the systemic circulation; and (iii) increase dissolution rate of poorly soluble drugs, which generally does not require the formulation to cross the mucosa or cells. doi: 10.1016/j.cocis.2008.01.002CrossRef Full Text | Google Scholar Ahmad, N., Alam, M. Design and evaluation of novel pH-sensitive chitosan nanoparticles for oral insulin delivery. J., Young, J. K., Mishra, P. In particular, they are usually transported to lysosomes for degradation. Improved oral bioavailability of alendronate via the mucoadhesive liposomal delivery system. Azoreductase activity of anaerobic bacteria isolated from human intestinal microflora. Mol. 91, 247–254. P., Wilson, C. doi: 10.1016/j.jconrel.2014.04.046PubMed Abstract | CrossRef Full Text | Google Scholar Larsson, J. The results have been promising, however further in vivo investigations are required in more clinically relevant animal models to determine the translatability and reproducibility of nanoparticulate formulations for gastric drug delivery. 48 (2-3), 139–157. Importantly, the total fraction of particles penetrating the rectal mucosa was relatively low in the study (Schmidt et al., 2013). H., Sharma, H. An Overview on Various Approaches and Recent Patents on Gastroretentive Drug Delivery Systems. D., Lybaert, L., Louage, B., De Koker, S., et al. doi: 10.1111/j.1365-2672.1991.tb02739.xPubMed Abstract | CrossRef Full Text | Google Scholar De Coen, R., Vanparijs, N., Risseeuw, M. For example, coating capsules or nanoparticles with pH sensitive polymers.Furthermore, the complexity in the design and development of new formulations should be minimized as much as possible for clinical translation to be justified (Hua et al., 2015; Hua et al., 2018). M., McConnell, E. doi: 10.1016/S0927-7765(99)00157-5CrossRef Full Text | Google Scholar Toorisaka, E., Watanabe, K., Ono, H., Hirata, M., Kamiya, N., Goto, M. doi: 10.1016/j.msec.2018.05.052PubMed Abstract | CrossRef Full Text | Google Scholar Kararli, T. Control Release 125 (2), 77–86. Drug Discovery Today 21 (7), 1155–1161. 294 (1-2), 247–259. pH-Degradable Mannosylated Nanogels for Dendritic Cell Targeting. J., Jain, A. R., Collier, K. doi: 10.1016/j.nantod.2017.08.006PubMed Abstract | CrossRef Full Text | Google Scholar Zhao, J., Li, X., Luo, Q., Xu, L., Chen, L., Chai, L., et al. Therefore, few have reached the clinic due to lack of specificity in drug release. 106 (Pt B), 256–276. Vaccine 16 (5), 536–541. PEG-functionalized microparticles selectively target inflamed mucosa in inflammatory bowel disease. J., O'Driscoll, C. doi: 10.1186/s40035-015-0041-1CrossRef Full Text | Google Scholar Hu, X., Fan, W., Yu, Z., Lu, Y., Qi, J., Zhang, J., et al. Further characterisation of the 'ileal brake' reflex in man–effect of ileal infusion of partial digests of fat, protein, and starch on jejunal motility and release of neurotensin, enteroglucagon, and peptide YY. Oral TNF-alpha gene silencing using a polymeric microsphere-based delivery system for the treatment of inflammatory bowel disease. Although preclinical studies of pH-dependent carriers for colon targeting have been promising, a major concern has been the inherent intra-individual and inter-individual variability of pH and emptying times from the GI tract as well as the change in luminal pH due to disease state.Biodegradable nanoparticulate formulations take advantage of the consistently high levels of resident bacteria and enzymes in the colon to trigger drug release (Bhavsar and Amiji, 2007; Moulari et al., 2008; Laroui et al., 2010; Kriegel and Amiji, 2011; Kriegel and Amiji, 2011; Laroui et al., 2014a; Xiao et al., 2014). (2015). Diet and the intestinal microbiome: associations, functions, and implications for health and disease. 32, 14–20. M. doi: 10.1016/j.jconrel.2015.12.008PubMed Abstract | CrossRef Full Text | Google Scholar Liu, L., Yao, W., Rao, Y., Lu, X., Gao, J. Prevalence of, and predictors of, bile acid malabsorption in outpatients with chronic diarrhea. K., Kansal, S., Garg, G., Awasthi, R., Singodia, D., Kulkarni, G. Eur. W., Savelkoul, P. T. G., Wu, G. This is likely to interfere with the adhesion of the nanoparticles with the mucosa. (USA: Pearson Benjamin Cummings). S., Mutalik, S. Transport of nanoparticles across an in vitro model of the human intestinal follicle associated epithelium. doi: 10.3389/fphar.2015.00286PubMed Abstract | CrossRef Full Text | Google Scholar Shahdadi Sardo, H., Saremnejad, F., Bagheri, S., Akhgari, A., Afrasiabi Garekani, H., Sadeghi, F. They reported a mean total mucosal surface area of approximately 32 m2 for the interior of the GI tract, with approximately 2 m2 representing the large intestine (Helander and Fandriks, 2014).The large intestine is the final major part of the GI tract. S., Bakhshaee, M., Stevens, H. This review will discuss the physiological, pathophysiological, and pharmaceutical considerations influencing drug delivery for the oral route of administration, as well as the conventional and novel drug delivery approaches. Azoreductase enzymes are largely produced by anaerobes present in the proximal part of the large intestine and onwards (Rafii et al., 1990; Oz and Ebersole, 2008; Marquez Ruiz et al., 2012).Pathological changes in the microflora can occur in diseases, such as IBD and gastrointestinal infections, as well as with the use of drugs (e.g., antibiotics) (Linskens et al., 2001; Sartor, 2010; Hua et al., 2015). (2004). Drug Delivery 1 (1), 141–163. These factors are dynamic, inter-related, and can further affect the efficacy of orally administered formulations. Drug Delivery 12 (9), 1389–1395. doi: 10.1016/j.bmcl.2012.10.006PubMed Abstract | CrossRef Full Text | Google Scholar Martinez, M. 280 (5), G922–G929. F., Adrian, T. The stomach and small intestine are the site of action for the major enzymes involved in the digestion of food (Marieb and Hoehn, 2010; Reinus and Simon, 2014). Biomaterials 33 (9), 2791–2800. Active Targeting of Drugs and Bioactive Molecules via Oral Administration by Ligand-Conjugated Lipidic Nanocarriers: Recent Advances. In addition, a variety of materials have been used to construct nanoparticles, including lipids and polymers. Immun. Additional in vivo studies are required to evaluate the efficacy and stability of different targeting ligands and formulations in animal models of colitis (Hua et al., 2015). G., Gullberg, E., Preat, V., Schneider, Y. The two main subtypes of IBD are Crohn's disease and ulcerative colitis (Podolsky, 2002). Orally delivered thioketal nanoparticles loaded with TNF-alpha-siRNA target inflammation and inhibit gene expression in the intestines. Nanoparticles and danger signals: Oral delivery vehicles as potential disruptors of intestinal barrier homeostasis. M., Tice, T. Controlled drug delivery formulations with prolonged gastric residence time can be advantageous for drugs that are absorbed in the small intestine, especially those with an absorption window in the upper small intestine (Streubel et al., 2006b). Alimentary Pharmacol. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Y., Seo, J. S., Evans, D. Reduction in particle size can also enhance targeting and uptake within diseased tissue in the colon. G., Eklund, E., Taha, Y., Raab, Y., Carlson, M. J., Wilding, I. This allows them to overcome the challenges faced by single-unit dosage forms, such as unpredictable disintegration and dissolution, nonspecific drug release, dose dumping, and stability issues in the GI tract (Talaei et al., 2013; Hua et al., 2015; Shahdadi Sardo et al., 2019). 299 (2), 775–781. doi: 10.1517/17425247.2014.927440CrossRef Full Text | Google Scholar Patel, M. H., Magosso, E., Barker, S. doi: 10.1111/j.1462-2920.2010.02294.xPubMed Abstract | CrossRef Full Text | Google Scholar Bratten, J., Jones, M. A., Ahmad, R., Umar, S., Jalees Ahmad, F. Role of the ileocecal junction in the motor response to intestinal resection. Sci. 11 (5), 1640–1650. S. Neurodegeneration 4, 18. Villi are finger-like projections that protrude into the intestinal lumen and are covered by epithelial cells. Floating dosage forms: an in vivo study demonstrating prolonged gastric retention. This may lead to the release of drug into a region where it has minimal absorption capacity or is easily degraded. E., Eliot, L. 136, 117–139. 14 (2), 155–161. doi: 10.1053/j.gastro.2014.01.056PubMed Abstract | CrossRef Full Text | Google Scholar Xiao, B., Yang, Y., Viennois, E., Zhang, Y., Ayyadurai, S., Baker, M., et al. F., Schulzke, J. Nanoparticles enhance therapeutic efficiency by selectively increased local drug dose in experimental colitis in rats. Role of nanoparticle size, shape and surface chemistry in oral drug delivery. doi: 10.1023/A:1016085108889CrossRef Full Text | Google Scholar Diesner, S. doi: 10.1016/S0031-6865(97)00050-2CrossRef Full Text | Google Scholar Rubinstein, A., Tirosh, B. doi: 10.1016/j.jconrel.2015.05.270PubMed Abstract | CrossRef Full Text | Google Scholar Thirawong, N., Thongborisute, J., Takeuchi, H., Sriamornsak, P. doi: 10.1016/j.jconrel.2005.10.031PubMed Abstract | CrossRef Full Text | Google Scholar Bargoni, A., Cavalli, R., Caputo, O., Fundaro, A., Gasco, M. S., Chitkara, D. Folate-decorated PLGA nanoparticles as a rationally designed vehicle for the oral delivery of insulin. Gastroenterology 139 (6), 1816–1819. Biol. Google Scholar Marquez Ruiz, J. 106 (Pt B), 367–380. For example, gastric pH can increase to 3–6 in the fed state. 184 (3), 1045–1059. Investigations into an alternate approach to target mannose receptors on macrophages using 4-sulfated N-acetyl galactosamine more efficiently in comparison with mannose-decorated liposomes: an application in drug delivery. doi: 10.1016/S0928-0987(97)10019-7CrossRef Full Text | Google Scholar Caraballo, I. Nano- and microparticulate drug carriers for targeting of the inflamed intestinal mucosa. Nanoparticles have a larger surface-area-to-volume ratio, which provides a greater surface area for interaction with the mucosal surface and for the solubilization of drugs. V., Merlin, D., Murthy, N. C., Mitragotri, S. doi: 10.1053/j.gastro.2013.01.047PubMed Abstract | CrossRef Full Text | Google Scholar Khan, M. Gastric transit time depends on many physiological factors, including age, body posture, gender, osmolarity, and food intake (Timmermans and Moes, 1994; Kagan and Hoffman, 2008). However, the prolonged nature of the dosage form would mean that immediate ceasing of a drug would be difficult, especially for patients experiencing adverse effects or hypersensitivity reactions.The formulation approaches for gastroretention have been extensively reviewed (Streubel et al., 2006a; Mandal et al., 2016; Awasthi and Kulkarni, 2016; Tripathi et al., 2019) and include the following: (i) high-density dosage forms that sink into the folds of the antrum; (ii) floating dosage forms over gastric content; (iii) mucoadhesive dosage forms to gastric mucosa; and (iv) expandable dosage forms which expand or swell in the stomach to larger dimensions. The colon is permanently colonized by an extensive number and variety of bacteria, which form the microbiome (Consortium, 2012; Reinus and Simon, 2014).Physiological Factors Influencing Oral Drug DeliveryDespite the clear advantages offered by the oral route, drug delivery can be challenging as the human GI tract is complex and displays a number of physiological barriers that affect drug delivery. The rapid and reversible absorption-enhancing effect of chitosan was suggested to be due to changes in intracellular pH caused by the activation of a chloride-bicarbonate exchanger, thereby resulting in the opening of the tight junctions (Rosenthal et al., 2012). (1991). Mechanisms of transport of polymeric and lipidic nanoparticles across the intestinal barrier. R., Rampton, D. Three main strategies are commonly used in conventional formulations for the regional delivery of drugs to the colon (Van den Mooter, 2006; Kagan and Hoffman, 2008; Vass et al., 2019): (i) utilization of a pH drop on entry into the colon; (ii) delayed release dosage forms that rely on gastrointestinal transit time; and (iii) exploitation of metabolic capabilities of the colonic microbiome.pH-Responsive Dosage FormsIn general, the first approach uses pH-specific coatings and matrices that are soluble at neutral or slightly alkaline pH to release the drug in the distal part of the small intestine or in the colon. doi: 10.1007/978-1-4757-2046-4_18PubMed Abstract | CrossRef Full Text | Google Scholar Eldridge, J. A., Brennan, J. Estimation of permeability by passive diffusion through Caco-2 cell monolayers using the drugs' lipophilicity and molecular weight. Nanoparticles that are internalized within enterocytes face additional challenges that restrict them from undergoing transcytosis. doi: 10.1016/0168-3659(90)90133-ECrossRef Full Text | Google Scholar Evans, D. The performance of these particular dosage forms is not dependent on the filling state of the stomach. I., Evora, C., Vila-Jato, J. doi: 10.1111/j.1572-0241.1999.01223.xPubMed Abstract | CrossRef Full Text | Google Scholar Cavalli, R., Bargoni, A., Podio, V., Muntoni, E., Zara, G. Interactions between targeting ligands and specific receptors expressed at the site of action are expected to improve bioadhesion of the carrier to specific cells and increase the extent for cellular uptake. Because solid dosage forms need to disintegrate and then dissolve the drug before absorption can occur, dissolution rate determines availability of the drug for absorption (Martinez and Amidon, 2002). Drug delivery to inflamed colon by nanoparticles: comparison of different strategies. Despite this variability, pH responsive approaches to colonic delivery have been used commercially. Y., Managuli, R. The difference is likely due to the gastroretentive strategy applied to the particles as well as the animal species used in the study. Drug Targeting 17 (3), 225–234. doi: 10.1016/j.biomaterials.2011.12.034PubMed Abstract | CrossRef Full Text | Google Scholar Rouge, N., Buri, P., Doelker, E. A. C., Hilal-Dandan, R. L., Smith, A. Adhesion to the proximal region of the duodenum would be most ideal, as the latter regions are exposed to boluses of digested food that are more solid in form, which can more readily detach the patch from the luminal surface (Banerjee and Mitragotri, 2017; Homayun et al., 2019). Therapeutic applications of hydrogels in oral drug delivery. 43 (12), 803–821. doi: 10.1002/1098-2299(200007/08)50:3/43.0.CO;2-5CrossRef Full Text | Google Scholar Sangalli, M. In addition, toxins secreted by intestinal pathogens can cause intestinal inflammation and increased epithelial permeability, which may alter the concentration of drugs in the colonic mucosa (Hoque et al., 2012; Hatton et al., 2018).In contrast, chronic diseases, such as inflammatory bowel disease (IBD), can cause significant changes to the physiology of the GI tract. C., Falson, F. Targeting polymerised liposome vaccine carriers to intestinal M cells. Non-starch polysaccharides are more resistant to digestion and absorption in the small intestine but are metabolized in the large intestine. Studies have also shown that the colonic pH in IBD patients can be highly variable in terms of disease progression and severity, with some patients having more acidic colonic pH in the range of 2.3–5.5 (Fallingborg et al., 1993; Sasaki et al., 1997; Nugent et al., 2001). 1 (3), 338–346. K., Rath, G. B., Ramteke, S., Jain, N. However, the size restriction needed for effective paracellular transport would limit most nanoparticulate formulations as well as the potential for toxicity with the passage of other gastrointestinal content in the chyme (Reinholz et al., 2018).Transcellular TransportTranscellular transport of nanoparticles across enterocytes is considered the most promising pathway for small intestinal drug delivery, owing to the large representation of these epithelial cells lining the GI tract (Reinus and Simon, 2014). E. Ideally, these dosage forms should be small enough to swallow and be able to rapidly increase in size once in the stomach to prevent premature emptying through the pylorus (Streubel et al., 2006b). 8 (2), 653–658. I., Langguth, P. doi: 10.1016/j.jconrel.2016.07.051PubMed Abstract | CrossRef Full Text | Google Scholar Banerjee, A., Pathak, S., Subramanium, V. For example, pH-dependent nanoparticulate formulations typically involve coating nanoparticles with pH-sensitive biocompatible polymers to trigger drug release in the colon and protect the incorporated active agents against the harsh gastrointestinal environment in the upper GI tract (Lamprecht et al., 2005b; Makhlof et al., 2009; Kshirsagar et al., 2012; Ali et al., 2014; Beloqui et al., 2014). 7, 4223–4237. doi: 10.3109/10837450.2011.557732PubMed Abstract | CrossRef Full Text | Google Scholar Kumar, M., Kaushik, D. Intestinal patches with an immobilized solid-in-oil formulation for oral protein delivery. (2013). doi: 10.1053/j.gastro.2010.10.036PubMed Abstract | CrossRef Full Text | Google Scholar Sasaki, Y., Hada, R., Nakajima, H., Fukuda, S., Munakata, A. 548 (1), 408–422. Biopharm Drug Dispos. The physiological changes associated with chronic inflammation of the GI tract should be considered in the development of improved oral delivery strategies for the management of IBD (Hua et al., 2015). 107 (10), 2663–2673. doi: 10.1016/S0378-5173(02)00004-2PubMed Abstract | CrossRef Full Text | Google Scholar Yang, L. 104 (34), 13780–13785. Curr. doi: 10.1021/acs.molpharmaceut.6b00877PubMed Abstract | CrossRef Full Text | Google Scholar Ali, H., Weigmann, B., Neurath, M. P., Labhasetwar, V., Amidon, G. K., Larauche, M., Duboc, H., Earle, K. Int. doi: 10.1080/10717544.2016.1199605PubMed Abstract | CrossRef Full Text | Google Scholar Jubeh, T., Barenholz, Y., Rubinstein, A. Current State and Future Perspectives on Gastroretentive Drug Delivery Systems. The highly acidic gastric environment (pH 1.5–2 in the fasted state) rises rapidly to pH 6 in the duodenum and increases along the small intestine to pH 7.4 at the terminal ileum (Fallingborg et al., 1993; Bratten and Jones, 2006). Acad. The major considerations for floating dosage forms are the susceptibility of the dosage form to body position (Timmermans and Moes, 1994) and the requirement to maintain a sufficient stomach content to allow an effective separation between the dosage form and the pyloric region (Whitehead et al., 1998; Kagan and Hoffman, 2008).Expandable dosage forms have garnered particular attention in recent years. Scand. (2002). doi: 10.1080/17474124.2018.1399794PubMed Abstract | CrossRef Full Text | Google Scholar Moulari, B., Pertuit, D., Pellequer, Y., Lamprecht, A. doi: 10.1016/0378-5173(96)85200-8CrossRef Full Text | Google Scholar Rouge, N., Allemann, E., Gex-Fabry, M., Balant, L., Cole, E. It consists of a capsule, half of which is enteric-coated and the other half is non-disintegrating. Nanoparticle-based clodronate delivery mitigates murine experimental colitis. C., et al. Control Release 116 (1), 1–27. (2005).

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