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Review Article

A REVIEW ON NOVEL APPROACHES FOR COLON TARGETED DRUG DELIVERY SYSTEM

Sharma Ankush*, Kanwar Kapil, Singh Amritpal, Pooja and Anju

CT Institute of Pharmaceutical Sciences, Shahpur, P.O. Udopur, Near Lambra,

Jalandhar-144020 Punajb, India.

ABSTRACT

The colon is a site where both local and systemic delivery of drugs can take place. Local delivery could, for example, allow topical treatment of inflammatory bowel disease. Treatment could be made more effective if it were possible for drugs to be targeted directly on the colon. Colon target drug delivery system has been gained great importance not only for the treatment of local diseases but also for the systemic delivery of proteins, therapeutic peptides, anti-asthmatic drugs, antihypertensive drugs and antidiabetic agents. However, recently continuous efforts have been taken on designing colon-specific delivery systems with improved site specificity and versatile drug release kinetics to accomplish different therapeutic needs. The focus of this review is to provide detailed insight into the conventional as well as recent approaches used to target the therapeutic agents specifically to the colon.

Keywords: Colon specific drug delivery, Conventional, Newly developed approaches.

INTRODUCTION

During the past decades research is going on in developing the methods to target the drug to the specific region. The goal of targeted drug delivery is to deliver the drug to the specific organ[1]. Colon targeted drug delivery is used to deliver the substances that are degraded by the digestive enzymes in the stomach such as proteins and peptides. It is also used for the treatment of various diseases like ulcerative colitis, crohn's disease, intestinal cancer, diarrhoea, for the treatment of diseases sensitive to circadian rhythms like Asthma, Angina, for the delivery of steroids, etc. Colon targeted drug delivery of drugs reduces the systemic side effects. Colon targeted drug delivery system increases the absorption of poorly absorbable drugs due to the high retention time of the colon[2].

ANATOMY AND PHYISOLOGY OF COLON

The GI tract is divided into stomach, small intestine and large intestine. The large intestine extending from the ileocecal junction to the anus is divided in to three main parts. These are the colon, the rectum and anal canal.

The entire colon is about 5 feet (150 cm) long, and is divided in to five major segments. Peritoneal folds called as mesentery which is supported by ascending and descending colon. The right colon consists of the cecum, ascending colon, hepatic flexure and the right half of the transverse colon. The left colon contain the left half of the transverse colon, descending colon, splenic flexure and sigmoid. The rectum is the last anatomic segment before the anus. The human intestine and colon were shown in (Figure1 and Figure 2).

The major function of the colon is the creation of suitable environment for the growth of colonic microorganisms, storage reservoir of faecal contents, expulsion of the contents of the colon at an appropriate time and absorption of potassium and water from the lumen. The absorptive capacity is very high, each about 2000ml of fluid

enters the colon through the ileocecal valve from which more than 90% of the fluid is absorbed[3].

Colonic Micro flora

The human alimentary canal is highly populated with bacteria and other microflora at the both ends, the oral cavity and the colon/rectum. In between these two sites, the GIT is very sparsely populated with microorganisms. Microorganisms of the oral cavity do not normally affect oral drug delivery systems and as such will not be considered here further. However, gut microflora of the colon have a number of implications in health and the treatment of disease such as IBD. The gut bacteria are capable of catalyzing a wide range of metabolic events. Many colon-specific drug delivery systems rely on enzymes unique to gut micro flora to release active agents in the colon. However, only two or three enzyme systems have been exploited in this area: azoreductases and glycosidases. A large number of polysaccharides are actively hydrolyzed by gut microflora leading to the possibility of using naturally occurring biopolymer as drug carriers. In addition, ethereal sulfate prodrugs or carboxylated prodrugs may be metabolized in the colon to the parent drug leading to local delivery in the colon. There is certainly room for innovative approaches to carry and release drugs in the colon based on the metabolic capabilities of the colon microflora. Azoreductases produced by colon play a central role in a number of delivery systems, most notably in catalyzing the release of 5-ASA from a variety of prodrugs. The second class of enzymes used to trigger the release of drugs in the colon is glycosidases. The main bacterial groups responsible for beta-glycosidases activity are lactobacilli, bacteroides and bifidobacteria. As with azo-reductase activity, the level of bacterial glycosidase activity in the gastrointestinal tract is associated with the concentration of bacteria in a given region[4].

Stomach and Intestinal pH

Generally, the release and absorption of orally administered drugs are influenced by the GI pH. The pH in differnat parts of the stomach and intestine is given in (Table 1).

Advantages of CDDS

Colon specific drug delivery system offers the following therapeutic advantages:-

1. Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, crohn's disease etc.)
2. Minimizing extensive first pass metabolism of steroids.
3. Preventing the gastric irritation produced by oral administration of NSAIDS.
4. Delayed release of drugs to treat angina, asthma and rheumatoid arthritis.
5. Drugs which are destroyed by the stomach acid and/or metabolized by pancreatic enzymes are slightly affected in the colon.
6. By producing the 'friendlier' environment for peptides and proteins when compared to upper gastrointestinal tract[5, 6].

Limitations and challenges in Colon Targeted Drug Delivery

1. The targeting of drugs to the colon is very complicated. Due to its location in the distal part of the alimentary canal, the colon is particularly difficult to access. In addition to that the wide range of pH values and different enzymes present throughout the gastrointestinal tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
2. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter.
3. The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.
4. One challenge in the development of colon-specific drug delivery systems is to establish an appropriate dissolution testing method to evaluate the designed system in-vitro. This is due to the rationale after a colon specific drug delivery system is quite diverse.
5. Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the fluid content in the colon is much lower and it is more viscous than in the upper part of the GI tract[7].

Approaches for colon targeted drug delivery[8]

1) Primary approaches for colon targeted drug delivery
    a. pH sensitive polymer coated drug delivery system
    b. Delayed release drug delivery system
    c. Microbially triggered drug delivery
        i. Prodrug approach
        ii. Polysaccharide based system

2) New approaches for colon targeted drug delivery
    a. Pressure controlled drug delivery system (PCDDDS)
    b. CODE
    c. Osmotic controlled drug delivery system (OROS-CT)
    d. Pulsatile
        i. Pulsincap system
        ii. Port system
    e. Azo hydrogels
    f. Multiparticulate system based drug delivery

1. (a) pH sensitive polymer coated drug delivery system

The pH varies in different parts of the gastrointestinal tract. The pH in stomach ranges between 1 and 2 during fasting. The pH in the proximal part of small intestine is 6.5 and in distal part of small intestine it is 7.5. The pH is6.4 in caecum, 5.7 in ascending colon, 6.6 intransverse colon and 7.0 in descending colon.The pH dependent drug delivery system is based on the solubility of different polymers at different pH ranges. The polymers are insoluble at lower pH values and get solubilizedas the pH increases.As the polymers are insoluble at lower pH values the polymer can protect a formulation in stomach and to some extent in small intestine. In this way by altering the polymers used the release of drug from the formulation can be controlled[9].

b) Delayed or time controlled release drug delivery system

Time controlled drug delivery system[10] includes sustained or delayed release systems. In this system the delayed release or colon targeted drug delivery is attained by prolonging the lag time. The transit time varies in different parts of gastrointestinal tract this transit time is responsible for the delayed release of drug.The main drawbacks of this delivery system are that the transit time varies from one.Person to another and amount of food intake. It also varies with paristalsis or contraction of gastrointestinal tract.

c) Microbially triggered drug delivery to colon

The microflora of colon is in the range of 1011 - 1012 CFU/mL, consisting main of anaerobic bacteria, e.g. Bacteroides, Bifidobacteria, Eubacteria, Clostridia, Enterococci, Enterobacteria and Ruminococcus etc. This vast microflora fulfills its energy needs by fermenting various types of substrates that have been left undigested in the small intestine. e.g. di- and tri-saccharides, polysaccharides etc[11]. For this fermentation the microflora produces a vast number of enzymes like glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase[12]. Because of the presence of the biodegradable enzymes only in the colon, the use of biodegradable polymers for colon-specific drug delivery seems to be a more site-specific approach as compared to other approaches[13]. These polymers shield the drug from the environments of stomach and small intestine and are able to deliver the drug to the colon. On reaching the colon, they undergo assimilation by micro-organism or degradation by enzyme or break down of the polymer back bone leading to a subsequent reduction in their molecular weight and thereby loss of mechanical strength. They are then unable to hold the drug entity any longer[14].

***(i)* Prodrug approach**

Prodrug is pharmacologically inactive derivative of a parent drug molecule that requires spontaneous or enzymatic transformation in-vivo to release the active drug.For colonic delivery the prodrug are designed to undergo minimal absorption and hydrolysis in the tracts of upper GIT and undergo enzymatic hydrolysis in the colon, there by releasing the active drug moiety from the drug carrier. Metabolism of azo compounds by intestinal bacteria is one of the most extensively studied bacterial metabolic processes[15]. A number of other linkages susceptible to bacterial hydrolysis especially in the colon have been prepared where the drug is attached to hydrophobic moieties like amino acids, glucoronic acids, glucose, galactose, cellulose etc. Limitations of prodrug approach is that it is not very versatile approach as it's formulation depends upon the functional group available on the drug moiety for chemical linkage. Further more prodrugs are new chemical entities

and need a lot of evaluation before being used as carriers[16].

***(ii)* Polysaccharide based system**

The polysaccharide which is polymer of monosaccharide retains their integrity, because they are resistant to digestive action of GI enzymes, matririces of polysachharide are assessed to remain intact in physiological environment of stomach and small intestine, as they reach colon they are acted upon bacterial polysaccharidases and results is degradation of the matrixes. Family of natural polysaccharide has appeal to area of drug delivery as it comprised of polymer with large number of derivitizable groups, with wide range of molecular weight, varying chemical composition and form most low toxicity and biodegradability,yet a high stability Pectin is a polysaccharide which contain α- 1,4 Dgalactouronic acid and 1,2 D- Rhamnose with D-galactose & D-arabinose Side chains. A novel colonic drug delivery is investigated. *In-vitro* experiments demonstrated that high methoxy pectin, when applied as compression coat, proved capable of coat tablet during condition stimulating gastrointestinal environment and was susceptible to enzymatic attack. *In-vivo* gamma scintigraphic studies confirmed the in-vitro findings the pectin coating tablets indicate that disintegrating in the colonic region, and illustrated that degradation by microflora, thus necessities in the development of such derivatives of pectin which is less water soluble, Calcium pectinate, the insoluble salt of pectin was used for colon targeted drug delivery of Indomethacin by Rubeinstein *et al*. The use of pectinolytic enzymes to stimulate breakdown in colon showed that pectin/chitosan mixture was susceptible to enzymatic breakdown and releasing its content. Mcleod *et al*., carried out a study to access the potential pectin: chitosan films for colonic delivery found that pectin alone was able to protect the premature release, but only when a substantially thick coat was provided[17].

2 (a) Pressure controlled drug delivery system (PCDDDS)

The digestive processes within the GI tract involve contractile activity of the stomach and peristaltic movements for propulsion of intestinal contents. In the large intestine, the contents are moved from one part to the next, as from the ascending to the transverse colon by forcible peristaltic movements commonly termed as mass peristalsis. These strong peristaltic waves in the colon are of short duration, occurring only three to four times a day.However, they temporarily increase the luminal pressure within the colon, which forms the basis for design of pressure-controlled systems. The luminal pressure resulting from peristaltic motion is higher in the colon compared to pressure in the small intestine, which is attributed to the difference in the viscosity of luminal contents. In the stomach and small intestine, contents are fluidic because of abundant water in digestive juices, but in the colon, the viscosity of the content is significantly increased due to reabsorption of water from the lumen and formation of feces. To author's knowledge,there is only one invention related to the development of pressure-controlled system for colonic delivery. This particular delivery system is in the form of a capsule, which is resistant to the pressures of the upper GI tract but is collapsed in the large intestine due to increased pressure. The capsule shells are fabricated from ethylcellulose and the collapse time of the capsule in the large intestine can be controlled by adjusting the thickness of the capsule shell wall. The preferred thickness of the capsule wall is about 35-60 μm[18].

(b) Osmotic controlled drug delivery system (OROS -CT)

The OROS-CT (Alza corporation) can be used to target the drug locally to the colon for the treatment of disease or to achieve systemic absorption that is otherwise unattainable. The OROS-CT system can be a single osmotic unit or may incorporate as many as 5-6 push-pull units, each 4 mm in diameter, encapsulated within a hard gelatin capsule, Each bilayer push pull unit contains an osmotic push layer and a drug layer, both surrounded by a semi permeable membrane. An orifice is drilled through the membrane next to the drug layer Immediately after the OROS-CT is swallowed, the gelatin capsule containing the push-pull units dissolves. Because of its drug-impermeable enteric coating, each push-pull unit is prevented from absorbing water in the acidic aqueous environment of the stomach, and hence no drug is delivered. As the unit enters the small intestine, the coating dissolves in this higher pH environment (pH >7), water enters the unit, causing the osmotic push compartment. Swelling of the osmotic push compartment forces drug gel out of the orifice at a rate precisely controlled by the rate of water transport through the semi permeable membrane. For treating ulcerative colitis, each push pull unit is designed with a 3-4 h post gastric delay to prevent drug delivery in the

small intestine[19]. Drug release begins when the unit reaches the colon. OROS-CT units can maintain a constant release rate for up to 24 hours in the colon or can deliver drug over a period as short as four hours. Recently, new phase transited systems have come which promise to be a good tool for targeting drugs to the colon. Various *in-vitro/in-vivo* evaluation techniques have been developed and proposed to test the performance and stability of CDDS. GI pressure is another mechanism that is utilised to initiate the release drug at distal part of GUT.

Mechanism

The muscular contraction of the GUT wall generates pressure, which is responsible for grinding and propulsion of the intestinal contents. The pressure generated varies in the intestine and duration throughout the GIT, with the colon considered to be having a higher luminal pressure due to the process that occurs during stool formation. System have therefore develop to resist the pressure of the upper GIT but rupture in the response to raised pressure of the colon[20]. Capsule shell fabricated from water- insoluble polymer has been used for this purpose. Performance of this system may be affected by administered food as it may disintegrate in stomach.

(c) Multiparticulate systems

Multiparticulates (pellets, non-peariles etc.) are used as drug carriers in pH-sensitive, time-dependent and microbially control systems for colon targeting. Multiparticulate systems have several advantages in comparison to the conventional single unit for controlled release technology, such as more predictable gastric emptying and fewer localized adverse effect than those of single unit tablets or capsules[21]. A multiparticulate dosage form was prepared to deliver active molecules to colonic region, which combines pH dependent and controlled drug release properties. This system was constituted by drug loaded cellulose acetate butyrate (CAB). Microspheres loaded by an enteric polymer (EudragitS). Here the enteric coating layer prevents the drug release below pH 7. After that CAB microspheres efficiently controlled the release of budesonide, which is depended on the polymer concentration in the preparation. Azo polymer coated pellets were used for colon-specific drug delivery to enhance the absorption of insulin and Eel calcitonin. A multiparticulate chitosan dispersed system (CDS) was prepared for colon drug delivery and it was composed of the drug reservoir and the drug release-regulating layer, which was composed of water insoluble polymer and chitosan powder. The drug reservoir was prepared by drug containing multiparticulates like Non peariles in the study. In this study the multiparticulate CDS was adopted not only for colon specific drug delivery but also for sustained drug delivery[22]. A multiparticulate system combining pH sensitive property and specific biodegradability was prepared for colon targeted delivery of metronidazole. The multiparticulate system was prepared by coating cross-linked chitosan microspheres exploring Eudragit L-100 and S-100 as pH sensitive polymers. The in-vitro drug release studies shows that no release of drug at acidic pH and higher drug release was found in presence of rat caecal contents indicating susceptibility of chitosan matrix to colonic enzymes released from rat caecal contents[23]. High-Amylose cornstarch and Pectin blend microparticles of diclofencac sodium for colon-targeted delivery were prepared by spray drying technique. The blending of high-amylose cornstarch with pectin improved the encapsulation efficiency and decreased the drug dissolution in the gastric condition from pectin-based microparticles. The drug released in colonic region by the action of pectinase from microparticles[24]. Masataka et al. investigated the effect of sodium glycocholate as an absorption promoter on orally administrated insulin absorption utilizing a colon-targeted delivery system. A novel insulin colon-targeted delivery system (Insulin- CODES) contains insulin, lactulose as a trigger for colon-specific release, citric acid as a solubilizer of insulin, meglumine as a pH adjusting agent and sodium glycocholate as an absorption promoter.

d. Azo-Polymeric Prodrugs

Newer approaches are aimed at the use of polymers as drug carriers for drug delivery to the colon. Both synthetic as well as naturally occurring polymers have been used for this purpose. Sub synthetic polymers have been used to form polymeric prodrug with azo linkage between the polymer and drug moiety[25]. These have been evaluated for CDDS.Various azo polymers have also been evaluated as coating materials over drug cores. These have been found to be similarly susceptible to cleavage by the azoreducatase in the large bowel. Coating of peptide capsules with polymers cross linked with azoaromatic group have been found to protect the drug from digestion in the stomach and small

intestine. In the colon, the azo bonds are reduced, and the drug is released[26]. (Table2)

Platform Technologies for CTDDS

1. PULSINCAP.
2. OROS-CT.
3. CODESTM.
4. PORT® SYSTEM.
5. TIME CLOCK® SYSTEM
6. CHRONOTROPIC® SYSTEM.
7. COLAL-PRED™.
8. TARGIT™TECHNOLOGY.
9. ENTERIONTM CAPSULE.
10. TICKING CAPSULE

Table 1: The pH in differnat parts of the stomach and intestine

Location	pH
Stomach	1.5 – 2.0
Fasted condition	3.0 – 5.0
Fed condition	5.0 – 6.0
Small intestine	6.0 – 7.5
Jejunesum	6.4
Ileum	6.7 – 7.3
Large intestine	6.4 – 7.0
Right colon	6.4
Mid colon and	6.6
Left colon	7.0

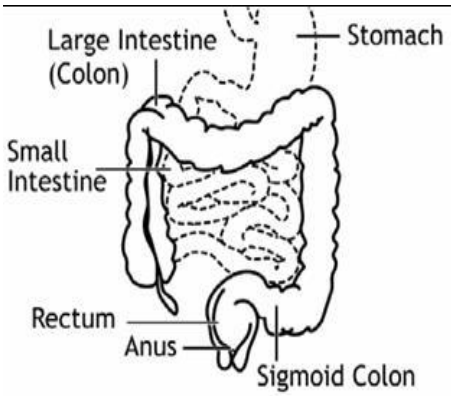

Fig. 1: Structure of human intestine

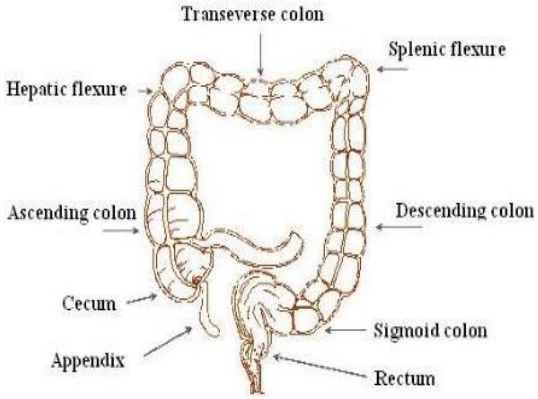

Fig. 2: Structure of colon

Table 2: Some azo polymer-based drug delivery systems evaluated for colon-specific drug delivery with summary of results obtained

Azo polymer	Dosage from prepared	Drug investigated	In-vitro/ in- vivo model used	Summary of the results obtained
Copolymers of styrene with 2-hydroxyethyl mrthacrylate	Coating over capsules	Vasopressin insulin	Rats dogs	These capsules showed biological respones characteristics of these peptide hormones in dog though it varied quantitatively[27]
Hydrogels prepared by copolymerization of 2-hydroxyethy1 methacrylate with 4-methacryloyloxy) azobenzene	Hydrogen	5-fluorouracil	In vitro	Drug release was faster and greater in human fecal media compared to simulated gastric and intestinal fluids[28]
Segmented polynurethanes	Coating over pellets	Budesonide	Rat	These azopolymer-coated pellets were useful for colon-specific delivery of budesonide to bring healing in induced colites71
Aromatic azo bond containing urethane analogues	Degradable films	5-ASA	In vitro degradation of films in presence of lactobacillus	These films were degraded by azoreductase. The permeability of 5-ASA from lactobacillus treated films was significantly higher than that of control[29]

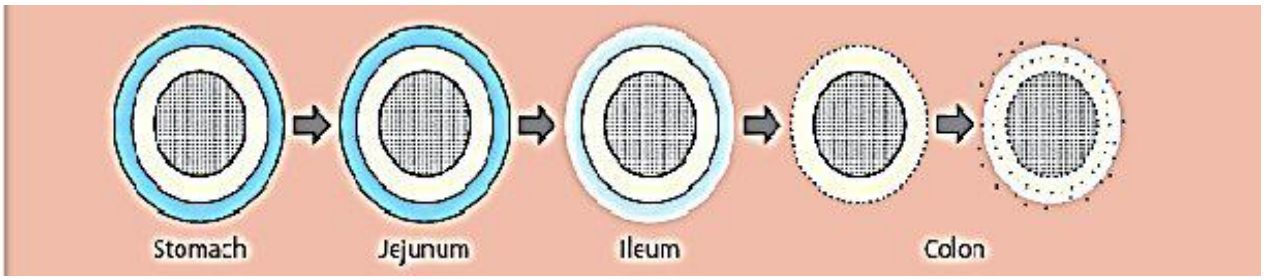

Fig. 3: Drug release pattern of a multilayer coated system at different pH conditions in GIT

CONCLUSION

The colonic region of the gastrointestinal tract has become an increasingly important site for drug delivery and absorption. Targeted drug delivery would offer considerable therapeutic benefits to patients, in terms of both local and systemic treatment. Systems that rely on gastrointestinal pH, transit times or pressure for release are unlikely to function as reliable and effective colon-specific delivery vehicles. Colon specificity is more likely to be achieved with systems that utilise natural materials that are degraded by bacterial enzymes of colonic origin. Moreover, the cost and ease of manufacture of the delivery system are further considerations that will impact on its likely commercialisation and hence, availability to patients. A bacteria-sensitive natural film coating that can be applied to a range of solid oral dosage forms using conventional processing technology would therefore appear to be the delivery system of choice.

FUTURE DEVELOPMENTS

Currently, there are several MR solid formulation technologies available for colonic delivery. These technologies rely on GI pH, transit times, enterobacteria and luminal pressure for site-specific delivery. Each of these technologies represents a unique system in terms of design but has certain shortcomings, which are often related to degree of site-specificity, toxicity, cost and ease of scale up manufacturing. It appears that microbiallycontrolled systems based on natural polymers have the greatest potential for colonic delivery, particularly in terms of sitespecificity and safety. In this, formulations that employ a film coating system based on the combination of a polysaccharide and a suitable film forming polymer represents a significant technological advancement. Further developments in this area require means to improve the coprocessing of the polymeric blend of a polysaccharide(s) and a film forming material. While, maintaining the propensity of the composition to microbial degradation in the colon. Earlier research indicates interest in colon site where, poorly absorbed drug molecules may have improved bioavailability. The distal colon is considered to have less hostile environment as well as enzyme activity compared to stomach and small intestine. The development of a dosage form that improves the oral absorption of drugs with low bioavailability because of instability in the GI tract (due to pH or enzymatic degradation) is one of the greatest challenges for oral delivery of drug in the pharmaceutical field. Colon targeted multiparticulate systems like microspheres and nanoparticles can provide a platform for delivery of drugs like peptides, proteins, oligonucleotides and vaccines. Therefore, more research has been focused on the specificity of drug uptake at the colon site. Such studies will be significant in advancing the cause of colon targeted delivery of therapeutics in future.

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