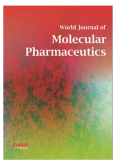

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REVIEW ARTICLE

Microspheres as a Carrier for Colon Targeting Drug Delivery System: A Review

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ABSTRACT

In the past ten years, there have been major advancements in medicine formulations that target the colon specifically. If a medicine could be administered directly to the colon, the effectiveness of the treatment might increase. Poorly soluble medications been proven to be absorbed in the colon. Because of their improved therapeutic efficacy and regulated drug release with fewer adverse effects, microspheres have become more important for drug delivery in the colon. This review briefly discusses colon introduction, various colon targeting strategies, and microspheres as a colon medication delivery system carrier.

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INTRODUCTION

Oral administration of drugs was found to be more suitable route of administration of drugs to the patient. The absorption of drugs given by oral route from the gastrointestinal tract (GIT) depends upon the various physical and chemical properties of the drugs. Nowadays new approaches have been made of delivering the drugs directly into the colon without exposure in the upper GI tract. These are known as Colon Specific drug delivery system (CDDS) or Targeted drug delivery system [1]. For the treatment of a number of bowels disorders such ulcerative colitis, Crohn's disease, amebiosis and colonic cancer targeted drug delivery into the colon is particularly desirable. The colon-specific drug delivery system (CDDS) should be able to protect the drug while it is being delivered to the colon; that is, the drug shouldn't be released or absorbed in the stomach or small intestine before it reaches the colon [2, 3].

To procure maximum therapeutic efficacy, it is important to deliver API to the target tissue in the optimal amount with in right period of time which reduce the toxicity and side effects. Several approaches are available which can deliver drugs to the target site [4, 5].

Advantages

- Ideal site for the delivery of active agents to cure the colon diseases (ulcerative colitis, Chron's diseases, amoebiasis, etc.).
- Optimum drug quantities should be required and improves patient compliance.
- Reduces frequency of dose and side effects [6].

Limitations

- Multiple manufacturing steps.
- Colonic performance may be impacted by local bacteria due to medication metabolism degradation.
- Incomplete release of drug Bioavailability of drug may be low due to potentially binding of drug in a nonspecific way to dietary residues, intestinal secretions, mucus or faecal matter [7].

Why Colon Is Targeted Drug Delivery Needed?

It is thought that colon-specific medication delivery systems are helpful in the treatment of colon disorders.

Direct treatment at the site of the disease, lower dosages, and fewer systemic side effects would all result from targeted medicine delivery to the colon.

Oral administration of peptide and protein medications would be possible using site-specific or targeted drug delivery systems. Colon-specific formulations might also be employed to extend the duration of the drug delivery.

If medications were specifically designed to treat the colon, a number of major colon disorders, such as ulcerative colitis, Crohn's disease, and colorectal cancer, might also be able to be treated more successfully [8, 9].

Anatomy of Colon

The GIT consists of parts from the mouth to the anus. It mainly consists of the stomach, small intestine, and large intestine [10].

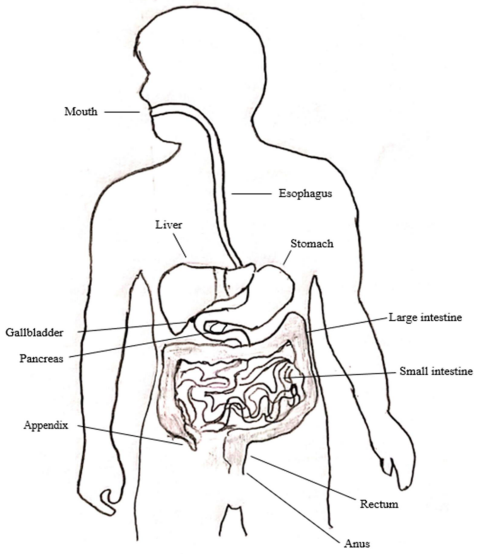

Figure 1: Human Digestive System

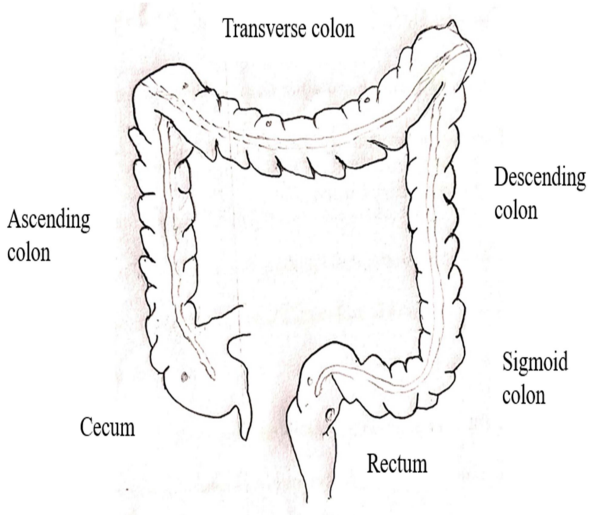

Figure 2: Anatomy of colon

Colon Comprises Four Sections

- The Ascending Colon: Length 20-25 cm
- This segment ascends from the caecum to the level of the liver before abruptly bending to the left at the hepatic flexure to produce the Transverse Colon.
- The Transverse Colon: Length 40-45 cm
- This segment forms the "splenic flexure" before abruptly bending downward to become the Descending Colon. It extends into the abdominal cavity in front of the stomach and duodenum to the spleen's location.
- Descending colon: Length 10-15 cm
- It passes through the left side of the abdominal cavity before bending in the middle. It is called the sigmoid colon if it is located on the iliac crest.
- The sigmoid colon: Length 35-40 cm
- This area describes the rectum, an S-shaped curve that descends from the pelvic cavity [11].

Colon pH

Varied people have varied GIT pH levels. The pH of the GIT is affected by factors like food intake, sickness, and more. The cornerstone for the creation of colon-targeted medication delivery devices is the alteration in pH in various GIT regions. To direct the medicine to the location, several polymers are coated [7].

pH of stomach is 1 -3
pH of small intestine is 5 – 7.5
pH of large intestine is 6.8 – 7.8
pH of rectum is 7.8 – 8

pH levels of different parts of GI tract are useful at the time of colon targeted formulation [12].

Colonic Microflora and Enzymes

The whole length of the human GIT is filled with both aerobic and anaerobic microorganisms in significant numbers. Numerous bacteria that create numerous enzymes required for metabolism can be found in the GIT. E. coli, Clostridia, Lactobacilli, Eubacteria, and Streptococci are just a few of the microorganisms that can release enzymes that are in charge of the many metabolic processes that occur in the GIT [7].

Transit of Material in the Colon

One of the most crucial considerations made while developing a formulation for the colon that is useful for determining the drug's residence there is the transit time of the drug [12].

Stomach shows transit time (hr) <1(fasting), 1>(fed)
Small intestine transit time (hr) 3-4 hr
Large intestine transit time (hr) 20-30.

Approaches used for Site-Specific Drug Delivery to Colon (CDDS) [2, 12, 13]

pH Sensitive Polymer Coated Drug Delivery to Colon

Give it a covering made of different pH-sensitive polymers to create a formulation with a delayed release and shield it from the upper GIT. Methacrylic acid copolymers, also referred to as Eudragit S 100, are the most widely used pH-dependent coating polymer. At pH levels higher than 7.0, it dissolves.

Delayed (Time Controlled Release System) Release Drug Delivery to Colon

A very promising method of medication release is the time-controlled release system (TCRS), which includes dose forms with delayed or sustained release. In these approaches, the colon arrival time of dose forms cannot be reliably predicted, leading to low colonic availability because of the possibly significant variability in gastric emptying time of dosage forms in humans. By extending the lag period by approximately 5 to 6 hours, the dosage forms may also be used as colon targeting dosage forms.

Microbially Triggered Drug Delivery to Colon

The colon's microflora is composed primarily of anaerobic bacteria, such as bacteroides, bifidobacteria, eubacteria, clostridia, enterococci, enterobacteria, and ruminococcus, and is in the range of 1011 -1012 CFU/mL. Various substrates, such as di- and tri-saccharides, polysaccharides, etc., that have been left undigested in the small intestine are fermented by this massive microflora to meet its energy requirements. Numerous enzymes, including glucoronidase, xylosidase, arabinosidase, galactosidase, nitroreductase, azareducatase, deaminase, and urea dehydroxylase, are produced by the microflora for this fermentation. Because biodegradable enzymes are exclusively present in the colon, using biodegradable polymers for colon-specific medication delivery appears to be a more site-specific strategy than other strategies. These polymers are able to transport the medicine to the colon while protecting it from the stomach and small intestine environments. They are broken down by enzymes, microorganisms, or the polymer's

backbone once they reach the colon, which causes their molecular weight to drop and their mechanical strength to decrease. The drug entity escapes from their grasp at that point.

Prodrug Approach for Drug Delivery to Colon

A prodrug is a chemically inert derivative of a parent molecule that needs to undergo an enzymatic change in the biological setting in order to release the active medication at the target site. In this method, the drug and its carrier are covalently linked such that when the medication is taken orally, the moiety stays intact in the stomach and small intestine. Once the drug reaches the colon, enzymatic cleavage regenerates the molecule.

Microspheres

Microspheres are tiny, spherical particles that typically have dimensions between one and one thousand micrometers. Microparticles are another name for microspheres. Numerous organic and synthetic substances can be used to make microspheres [1].

Compared to traditional multi-dose therapy, advanced drug delivery systems have a number of benefits. The drug delivery methods in the microsphere are suitable for formulations with achieved delay or sustained release with little chance of dose repetition and brief gastric occupancy time [14].

Advantages of Microspheres

- A consistent and extended therapeutic impact is provided by microspheres.
- By lowering the dose frequency, microspheres increase patient compliance.
- Microspheres offer a regulated, sustained, and precise medication delivery.
- Microspheres reduce dose dumping.
-

Limitations of Microspheres

- The rate of controlled release of microspheres may vary depending on intrinsic or external factors like diet, gut transit time, mucin turnover rate, etc.
- There are differences in release from one to another dosage form.
- In the case of parentral microspheres, minimal drug loading is performed [15].

Types of Microspheres

Bioadhesive Microspheres

Adhesion is the attachment of a substance to a membrane using the adhesive properties of water-soluble polymers. adhesion to the mucosal membranes of the drug delivery device, including the buccal, ophthalmic, rectal, nasal, etc. These kinds of microspheres stay at the application site for a long time, interact closely with the absorption site, and produce greater therapeutic results. Extended contact time with mucoadhesive microspheres at the application or absorption site increases or improves the therapeutic efficacy of the medicine [4].

Magnetic Microspheres

This type of delivery mechanism, which targets the drug to the site of the ailment, is crucial. In this case, a smaller amount of a medicine that is magnetically targeted can replace a larger amount of a drug that is freely circulating. Materials utilized for magnetic microspheres such as chitosan and dextran are integrated into magnetic carriers, which receive magnetic responses to a magnetic field.

The different types of magnetic microspheres are as follows:

Therapeutic Magnetic Microspheres:

These are used to deliver chemotherapeutic agent to liver tumor. Drugs like proteins and peptides can also be targeted through this system.

Diagnostic Microspheres:

They can be used for imaging liver metastases and also can be used to distinguish bowel loops from other abdominal structures by forming nano size particles superparamagnetic iron oxides.

Floating Microspheres

Because the bulk density of floating kinds is lower than that of gastric fluid, they float unaffected by the rate at which the stomach empties. If the system is floating on stomach content and increases gastric residence and increases plasma concentration fluctuation, the medicine is released slowly at the desired rate. Additionally, it lessens the likelihood of striking and dose dumping. It also results in a sustained therapeutic impact, which lowers the frequency of dose. Ketoprofen is administered using this form.

Radioactive Microspheres

When microspheres larger than capillaries (10–30 nm) come into contact with them, they tap into the first capillary bed. They are injected into

the arteries that supply the target tumor. Radioactive microspheres therefore deliver substantial radiation doses to the targeted locations under all of these circumstances without harming the normal surrounding tissues. It is different from medication delivery systems in that radioactivity is not discharged from the microspheres but rather acts from a distance that is characteristic for radioisotopes, and the various types of radioactive microspheres are emitters, emitters, emitters.

Polymeric Microspheres

The various varieties of polymeric microspheres can be divided into following classes.

Biodegradable Polymeric Microspheres

The idea behind the usage of natural polymers like starch is that they are biodegradable, biocompatible, and naturally sticky. Due to their extreme swelling capacity in aqueous media, biodegradable polymers extend their time in contact with mucous membranes, causing gel to develop. The concentration of the polymer and the sustained release pattern regulate the rate and degree of medication release. The key disadvantage is that biodegradable microspheres' drug loading efficiency in clinical settings is complex, making it challenging to regulate drug release. However, they have numerous applications in treatments based on microspheres.

Synthetic Polymeric Microspheres

In addition to being employed as bulking agents, fillers, embolic particles, drug delivery vehicles, and other things in clinical settings, synthetic polymeric microspheres have also shown to be safe and biocompatible. However, the fundamental drawback of these microspheres is that they frequently migrate away from the injection site, increasing the risk of embolism and subsequent organ damage [16].

Method of Preparation

- Spray Drying Technique
- Solvent Evaporation
- Single emulsion technique
- Double emulsion technique
- Spray drying
- Coacervation Method
- Solvent extraction
- Ionic gelation

Characterization and Evaluation of Microspheres

Micromeritic Properties

In micromeritic properties bulk density, tapped density, carr's index, hausner's ratio and angle of repose are evaluated.

Molecule Size and Shape

Scanning Electron Microscopy (SEM) is used to determine the size and shape of the microsphere [14].

Fourier Transform Infrared Spectroscopy

Drug polymer interaction and degradation of microspheres can be assessed by FTIR [15].

Percentage Yield

The weight of the dried product at room temperature divided by the theoretical amount was used to calculate the yield of the prepared formulations [7]. Product yield is calculated by using the following Equation:

$$\text{Product yield} = \frac{\text{Weight of the product}}{\text{Weight of raw materials}} \text{ X } 100$$

Drug Entrapment Efficiency

Crushed microspheres are obtained and weighed in quantity. Afterward, it was stirred into a buffer solution before being dissolved and filtered. Utilizing a calibration curve, the UV spectrophotometer measures the filtrate at a certain wavelength [15, 17-18].

***In-vitro* Dissolution Test**

The conventional basket method is used to conduct the dissolving tests. Dissolution testing is carried out in buffers with a range of pH values in order to assess formulations at various pH levels. Several media that simulate gastric fluid (pH 1.2), the small intestine (pH 6.8), and the large intestine (pH 7.4) are utilized for the dissolution testing of colon-targeted drug delivery. The three environments that the colon targeted medication delivery systems are put through last for two hours each. The first environment has a pH of 1.2 (0.1N HCl), the second has a pH of 6.8 (phosphate buffer), and the third has a pH of 7.4 (phosphate buffer). to evaluate colon-specific medication delivery methods [19-25].

Table 1: Examples of microspheres for colon targeting

Drug	Polymer used	Purpose
Mesalamine	Chitosan microspheres coated with Eudragit S100	Treatment of Ulcerative colitis [26]
Curcumin	Guar Gum, Xanthan Gum	Treatment of Colon cancer [27]
Satranidazole	Eudragit S100	Ulcerative Colitis, Amoebiasis, Chron's Disease, Carcinomas & Infections [28]
Capecitabine	Eudragit L 100, Eudragit S 100	Colorectal Cancer [29]
Zidovudine	Chitosan	HIV And AIDS Related Conditions [30]
Meloxicam	Sodium Alginate Coated with Eudragit S100	Colorectal Cancer [31]
Glipizide	Eudragit S 100	Treatment Of Type II Diabetes [32]
Diclofenac Sodium	Diclofenac Sodium	Treatment Of Arthritis [33]
Piroxicam	Sodium Alginate Microspheres Coated with Eudragit S 100	Treatment Of Rheumatoid Arthritis [34]
Aceclofenac	Sodium Alginate Microspheres Coated with Cellulose Acetate Phthalate	Used In Treatment Rheumatoid Arthritis Diseases [35]

CONCLUSION

Microspheres offer more benefits when used in colon drug delivery systems. The main advantage of microspheres is that they increase therapeutic efficacy and reduce side effects. Colon drug delivery can be achieved by using various approaches by which a drug can be delivered to the colon with the help of microspheres as a carrier. So, microspheres are a useful approach to be used for colon drug delivery.

REFERENCES

[1] Singh A., Sharma A., Kaur S., "Micro carrier as colon drug delivery system: A review", Int. J. Res. Dev. Pharm. L. Sci., 2014, 3(6), pp. 1211-1216.

[2] Philip AK, Philip B. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Medical Journal. 2010;25(2):79.

[3] Mabrouk M, Bijukumar D, Mulla JA, Chejara DR, Badhe RV, Choonara YE, Kumar P, du Toit LC, Pillay V. Enhancement of the biomineralization and cellular adhesivity of polycaprolactone-based hollow porous microspheres via dopamine bio-activation for tissue engineering applications. Materials Letters. 2015 Dec 15;161:503-7.

[4] Shaikh K., Review On: Colon Targeted Microspheres. International Journal of Pharmaceutical Research and Applications Volume 8, Issue 1 Jan-Feb 2023, pp: 278-290.

[5] Mulla JAS, Aralelimath VR, Tipugade O, Shinde SS, Tetgure NG, Mulla AA, Gavali DD. Formulation and Evaluation of Teneligliptin-Loaded Mucoadhesive Microspheres. Indian Journal of Novel Drug Delivery. 2020Oct-Dec;12(4): 222-227.

[6] Anita, Singh A and Dabral A: A review on colon targeted drug delivery system. Int J Pharm Sci & Res 2019; 10(1): 47-56. doi: 10.13040/ IJPSR.0975-8232.10(1).47-56.

[7] Abhishek SB, Parthiban S, Kumar GS, Mani TT. Microparticle as Suitable Drug Carriers for Colon Targeting–A Recent Review. American Journal of PharmTech Research. 2018;8(1):45-6.

[8] Qureshi AM, Momin M, Rathod S, Dev A, Kute C. Colon targeted drug delivery system: A review on current approaches. Indian Journal of Pharmaceutical and Biological Research. 2013 Oct 31;1(4):130-47.

[9] Kumar SP, Prathibha D, Parthibarajan R, Reichal CR. Novel colon specific drug delivery system: A review. International Journal of Pharmacy and Pharmaceutical Sciences. 2012; 4(1):22-9.

[10] Sunday OS. Colon specific drug delivery systems: current trends and approaches. Universal Journal of Pharmaceutical Research. 2017;2(4):53-7.

[11] Nareshkumar SA, Raval AG. Formulation and evaluation of colon targeted pellets of bumadizone calcium. International Journal of Pharmaceutical and Biological Science Archive. 2019;7.
[12] Bansode AS. International Imperial Journal of Pharmaceutics & Cosmetology.
[13] Rutuja P. Bugad, Sachinkumar V. Patil. A comprehensive review on colon targeted drug delivery system. International Journal of Creative Research Thoughts 2021; 9 (7): 225 - 237.
[14] Gavhane P, Deshmukh M, Khopade AN, Kunjir VV, Shete RV. A review on microsphere. Journal of Drug Delivery and Therapeutics. 2021 Jan 15;11(1):188-94.
[15] Sharma N, Purwar N, Gupta PC. Microspheres as drug carriers for controlled drug delivery: a review. International Journal of pharmaceutical sciences and research. 2015 Nov 1;6(11):4579.
[16] Gavali KV, Kengar MD, Chavan KV, Anekar VP, Khan NI. A Review on Microsphere and its Application. Asian Journal of Pharmaceutical Research. 2019;9(2):123-9.
[17] Mulla JA, Mabrouk M, Choonara YE, Kumar P, Chejara DR, du Toit LC, Pillay V. Development of respirable rifampicin-loaded nano-lipomer composites by microemulsion-spray drying for pulmonary delivery. Journal of Drug Delivery Science and Technology. 2017 Oct 1;41:13-19.
[18] Panchamukhi SI, Mulla JA, Shetty NS, Khazi MI, Khan AY, Kalashetti MB, Khazi IA. Benzothieno [3, 2-e][1, 2, 4] triazolo [4, 3-c] pyrimidines: Synthesis, Characterization, Antimicrobial Activity, and Incorporation into Solid Lipid Nanoparticles. Archiv der Pharmazie. 2011 Jun;344(6):358-65.
[19] Dubey, Neha & Dubey, Gaurav & Ali, Jamshed. (2021). A Comprehensive Review on Colon Targeted Drug Delivery System. World Journal of Pharmacy and Pharmaceutical Sciences. 10. 2322-2340.
[20] Mulla JAS, Shetty NS, Panchamukhi SI, Khazi IAM. Formulation, Characterization and *in vitro* Evaluation of Novel Thienopyrimidines and Triazolothienopyrimidines Loaded Solid Lipid Nanoparticles. International Journal of Research in Ayurveda & Pharmacy. 2010; 1(1): 192-200.
[21] Mulla JA, Suresh S, Khazi IA. Formulation, characterization and in vitro evaluation of methotrexate solid lipid nanoparticles. Research J. Pharm. and Tech. 2009 Oct;2(4):685-9.
[22] Mulla JA, Khazi MI, Khan AY, Gong YD, Khazi IA. Design, Characterization and In vitro Evaluation of Imidazo [2, 1-b][1, 3, 4] thiadiazole Derivative Loaded Solid Lipid Nanoparticles. Drug Invention Today. 2012 Aug 1;4(8).
[23] Mandal S, Ratan GN, Mulla JS, Thimmasetty J, Kaneriya A. Design and In Vitro Evaluation of Gastro Retentive Sustained Release Tablets of Tizanidine Hydrochloride. Indian Journal of Novel Drug delivery. 2010; 2(4): 144-152.
[24] Mabrouk M, Mulla JA, Kumar P, Chejara DR, Badhe RV, Choonara YE, du Toit LC, Pillay V. Intestinal targeting of ganciclovir release employing a novel HEC-PAA blended lyomatrix. AapsPharmscitech. 2016 Oct;17(5):1120-30.
[25] Mabrouk M, Chejara DR, Mulla JA, Badhe RV, Choonara YE, Kumar P, Du Toit LC, Pillay V. Design of a novel crosslinked HEC-PAA porous hydrogel composite for dissolution rate and solubility enhancement of efavirenz. International journal of pharmaceutics. 2015 Jul 25;490(1-2):429-37.
[26] Badhana S, Garud N, Garud A. Colon specific drug delivery of mesalamine using eudragit S100-coated chitosan microspheres for the treatment of ulcerative colitis. International Current Pharmaceutical Journal. 2013 Feb 2;2(3):42-8.
[27] Vajpayee A, Fartyal S, Singh AP, Jha SK. Formulation and evaluation of colon targeted curcumin microspheres using natural polymers. J Pharm Res Opinion. 2011;1:108-2.
[28] Chandra D, Yadav I, Singh H Jain DA. Design and development of satranidazole microspheres for colon targeted drug delivery. IJPCS. 2012; 1(3):1510-1516.
[29] Agarwal D, Ranawat MS, Chauhan CS, Kamble R. Formulation and characterisation of colon targeted pH dependent microspheres of capecitabine for colorectal cancer. Journal of Drug Delivery and Therapeutics. 2013;3(6):215-22.
[30] Priyadarshini MK, S Parthiban, Gp Senthil Kumar, T Tamizh Mani. Formulation And Evaluation of Microspheres Encapsulating Zidovudine by Ionic Gelation Techniques. International Journal of Research in

Pharmaceutical and Nano Sciences. 3(5), 2014, 461- 468.

[31] Kumar S, Parthiban S, Kumar SS. Formulation and evaluation of meloxicam loaded microspheres for colon targeted drug delivery. 4 (2). 2013:80-9.

[32] Gourav G, Payal G, Gurdev S, Sapna S, Renu B, Jyoti R, Sunaina A. Synthesis and Characterization Of Colonic Microspheres Of Glipizide By Ionic Gelation Method. Indo American Journal of Pharmaceutical Research. 2016;6(11):7129-35.

[33] Christina E. Preparation of Microspheres of Diclofenac Sodium by Ionotropic Gelation Technique. International Journal of Pharmacy and Pharmaceutical Sciences. 2013; 5(1):228-231.

[34] Madhavi K, Dr Rani S, Zahra F. Formulation And *In Vitro* Evaluation of Piroxicam Loaded Alginate Microspheres (Colon Specific) Using Ionotropic Gelation Technique. Iosr Journal of Pharmacy. 2016; 6(3):23-28.

[35] Rk B, Agrawal S, Pathan JK, Dubey PK. Formulation and Evaluation of a Novel Drug Delivery System of Aceclofenac for Colonic Drug Delivery. Journal Of Pharmacy Research. 2012;5(1):108-12.