International Journal of Current Trends in Pharmaceutical Research

Journal Home Page: www.pharmaresearchlibrary.com/ijctpr

Review Article **Open Access**

Recent Marketed Products used in Novel Drug Delivery System

Pranit Saraswat*, Ritesh Kumar Tiwari, Pragati Khare and Priyanka Bhatt

Department of Pharmacy, Shri Ram Murti Smarak College of Pharmacy, Bareilly.

A B S T R A C T

The goal of any ideal drug delivery system is to provide a therapeutic amount of drug to the proper site in the body to achieve prompt response, and thus maintain the desired drug concentration. Such a conceptualized ideal drug delivery can be possible with intravenous infusion of drug at the site of action over a desired period of time. The aim of this study to different marketed product which is use in various drug delivery systems like Controlled release drug delivery and Transdermal drug delivery, the colon is a site where both local and systemic delivery of drugs can take place. Local delivery allows topical treatment of inflammatory bowel disease. However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects. Controlled release dosage forms cover a wide range of prolonged action formulations, which provide continuous release of their active ingredients at a predetermined rate and time. The majority of these formulations are designed for oral administration. In Transdermal drug delivery system the delivery of drugs across the skin and into systemic circulation. A Transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the systemic circulation.

Keywords: Colon drug delivery system, Transdermal drug delivery, Marketed product.

A R T I C L E I N F O

CONTENTS

Article History: Received 28 November 2016, **Accepted** 19 December 2016, **Available Online** 15 January 2017

***Corresponding Author**
Pranit Saraswat
Department of Pharmacy,
Shri Ram Murti Smarak
College of Pharmacy, Bareilly.
Manuscript ID: IJCTPR3267

PAPER-QR CODE

Citation: Pranit Saraswat, *et al.* Recent Marketed Products used in Novel Drug Delivery System. *Int. J. Curnt. Tren. Pharm, Res.*, 2017, 5(1): 49-55.

1. Introduction

The method by which a drug is delivered can have a significant effect on its efficacy. Some drugs have an optimum concentration range within which maximum benefit is derived, and concentrations above or below this range can be toxic or produce no therapeutic benefit at all. On the other hand, the very slow progress in the efficacy of the treatment of severe diseases, has

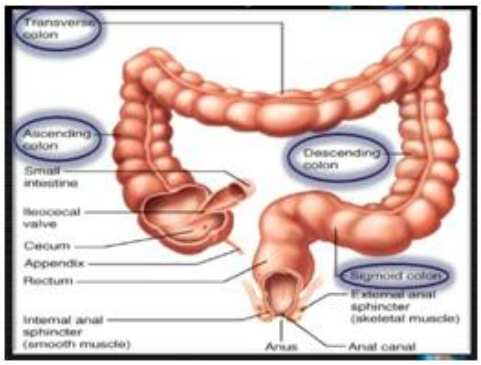

Figure 1: Anatomy of colon

Suggested a growing need for a multidisciplinary approach to the delivery of therapeutics to targets in tissues. From this, new ideas on controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs were generated. [1] These new strategies, often called drug delivery systems (DDS), are based on interdisciplinary approaches that combine polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology. [2] To minimize drug degradation and loss, to prevent harmful side-effects and to increase drug bioavailability and the fraction of the drug accumulated in the required zone, various drug delivery and drug targeting systems are currently under development. [3]

The carriers can be made slowly degradable, stimuli-reactive (pH- or temperature-sensitive), and even targeted (e.g., by conjugating them with specific antibodies against certain characteristic components of the area of interest). Targeting is the ability to direct the drug-loaded system to the site of interest. The anatomy of colon is shown in Fig.1. Two major mechanisms can be distinguished for addressing the desired sites for drug release: Passive and Active targeting. [4]

Potential release mechanisms involve:

- Desorption of surface-bound /adsorbed drugs;
- Diffusion through the carrier matrix;
- Diffusion (in the case of nanocapsules) through the carrier wall
- Carrier matrix erosion
- A combined erosion /diffusion process.

The mode of delivery can be the difference between a drug's success and failure, as the choice of a drug is often influenced by the way the medicine is administered. Sustained (or continuous) release of a drug involves polymers that release the drug at a controlled rate due to diffusion out of the polymer or by degradation of the polymer over time. Pulsatile release is often the preferred method of drug delivery, as it closely mimics the way by which the body naturally produces hormones such as insulin. It is achieved by using drug-carrying polymers that respond to specific stimuli (e.g., exposure to light, changes in pH or temperature). This has been indicated in Fig. 2.

Advantages of controlled drug delivery system over a conventional dosage form

1. Improved patient convenience and compliance due to less frequent drug administration.
2. Reduction in fluctuation in steady – state levels and therefore-
    - Better control of disease condition and
    - Reduced intensity of local or systemic side effects
3. Increased safety margin of high potency drugs due to better control of plasma levels.
4. Maximum utilization of drug enabling reduction in total amount of dose administered.
5. Reduction in health care cost through-
    - Improved therapy.
    - Shorter treatment period.
    - Lower frequency of dosing.[5]

Disadvantages of controlled drug delivery system

1. Decreased systemic availability in comparison to immediate release conventional dosage forms. this may be due to-
    a. Incomplete release.
    b. Increased first pass metabolism.
    c. Increased instability.
    d. Site specific absorption.
    e. PH dependent solubility.
2. Poor in vitro- in vivo correlation.
3. Reduced potential for dosage adjustment of drugs normally administered in varying strengths.
4. Higher cost of formulation.[6]

2. Criteria for Selection of Drug for CDDS

The best Candidates for CDDS are drugs which show poor absorption from the stomach or intestine including peptides. The drugs used in the treatment of IBD, ulcerative colitis, diarrhea, and colon cancer are ideal candidates for local colon delivery. The criteria for selection of drugs for CDDS are summarized in Table 1. Drug Carrier is another factor which influences CDDS. The selection of carrier for particular drugs depends on the physiochemical nature of the drug as well as the disease for which the system is to be used. Factors such as chemical nature, stability and partition coefficient of the drug and type of absorption enhancer chosen influence the carrier selection [7] [8]. Moreover, the choice of drug carrier depends on the functional groups of the drug molecule. For example, aniline or nitro groups on a drug may be used to link it to another benzene group through an azo bond. The carriers, which contain additives like polymers (may be used as matrices and hydro gels or coating agents) may influence the release properties and efficacy of the systems. [9]

Approaches used for Site Specific Drug Delivery to Colon (CDDS): Several approaches are used for site-

specific drug delivery. Among the primary approaches for CDDS, These include:

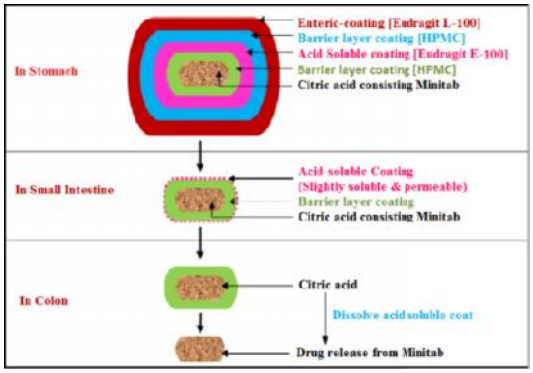

Figure 2: Systematic diagram of drug release in colon

1) Primary Approaches for CDDS

A. pH Sensitive Polymer Coated Drug Delivery to the Colon: In the stomach, pH ranges between 1 and 2 during fasting but increases after eating. The pH is about 6.5 in the proximal small intestine and about 7.5 in the distal small intestine. [10] From the ileum to the colon, pH declines significantly. It is about 6.4 in the caecum. However, pH values as low as 5.7 have been measured in the ascending colon in healthy volunteers. [11] The pH in the transverse colon is 6.6 and 7.0 in the descending colon. Use of pH dependent polymers is based on these differences in pH levels The polymers described as pH dependent in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. [12]. Examples of marketed products of pH dependent system are indicated in Table 2. Although a pH dependent polymer can protect a formulation in the stomach, and proximal small intestine, it may start to dissolve in the lower small intestine, and the site-specificity of formulations can be poor. The decline in pH from the end of the small intestine to the colon can also result in problems, lengthy lag times at the ileo-caecal junction or rapid transit through the ascending colon which can also result in poor site-specificity of enteric-coated single-unit formulations. **[13]**

B. Delayed (Time Controlled Release System) Release Drug Delivery to Colon: Time controlled release system (TCRS) such as sustained or delayed release dosage forms are also very promising drug release systems. However, due to potentially large variations of gastric emptying time of dosage forms in humans, in these approaches, colon arrival time of dosage forms cannot be accurately predicted, resulting in poor colonical availability. The dosage forms may also be applicable as colon targeting dosage forms by prolonging the lag time of about 5 to 6 h. However, the disadvantages of this system are:

- Gastric emptying time varies markedly between subjects or in a manner dependent on type and amount of food intake.
- Gastrointestinal movement, especially peristalsis or contraction in the stomach would result in change in gastrointestinal transit of the drug.
- Accelerated transit through different regions of the colon has been observed in patients with the IBD, the carcinoid syndrome and diarrhea, and the ulcerative colitis. [14, 15]

2. Newly Developed Approaches for CDDS

a. Pressure Controlled Drug-Delivery Systems

As a result of peristalsis, higher pressures are encountered in the colon than in the small intestine. Takaya et al. developed pressure controlled colon-delivery capsules prepared using ethyl cellulose, which is insoluble in water. **[16]** In such systems, drug release occurs following the disintegration of a water-insoluble polymer capsule because of pressure in the lumen of the colon. The thickness of the ethylcellulose membrane is the most important factor for the disintegration of the formulation [17]. The system also appeared to depend on capsule size and density. Because of reabsorption of water from the colon, the viscosity of luminal content is higher in the colon than in the small intestine. It has therefore been concluded that drug dissolution in the colon could present a problem in relation to colon-specific oral drug delivery systems. In pressure controlled ethyl cellulose single unit capsules the drug is in a liquid. **[18]** Lag times of three to five hours in relation to drug absorption were noted when pressure-controlled capsules were administered to humans.

b. Novel Colon Targeted Delivery System (CODESTM)

CODESTM is a unique CDDS technology that was designed to avoid the inherent problems associated with pH or time dependent systems. [19] CODESTM is a combined approach of pH dependent and microbially triggered CDDS. It has been developed by utilizing a unique mechanism involving lactulose, which acts as a trigger for site specific drug release in the colon. The system consists of a traditional tablet core containing lactulose, which is over coated with and acid soluble material, Eudragit E, and then subsequently overcoated with an enteric material, Eudragit L. The marketed products of osmotic systems are indicated in Table 3.

3. Transdermal Drug Delivery System

Optimum therapeutic outcomes require not only proper drug selection but also effective drug delivery. The human skin is a readily accessible surface for drug delivery. Over the past three decades, developing controlled drug delivery has become increasingly important in the pharmaceutical industry. The pharmacological response, both the desired therapeutic effect and the undesired adverse effect, of a drug is dependent on the concentration of the drug at the site of action, which in turn depends upon the dosage form and the extent of absorption of the drug at the site of action.

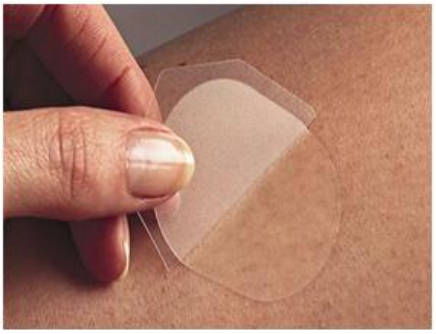

Figure 3: Transdermal patch

Skin of an average adult body covers a surface of approximately 2 m 2 and receives about one-third of the blood circulating through the body. Skin contains an uppermost layer, epidermis which has morphologically distinct regions; basal layer, spiny layer, stratum granulosum and upper most stratum corneum, it consists of highly cornified (dead) cells embedded in a continuous matrix of lipid membranous sheets. These extracellular membranes are unique in their compositions and are composed of ceramides, cholesterol and free fatty acids. The transdermal patch is shown in Fig 3. The human skin surface is known to contain, on an average, 10-70 hair follicles and 200-250 sweat ducts on every square centimeters of the skin area. It is one of the most readily accessible organs of the human body. The potential of using the intact skin as the port of drug administration to the human body has been recognized for several decades, but skin is a very difficult barrier to the ingress of materials allowing only small quantities of a drug to penetrate over a period of time. [20]

Advantages of Transdermal Drug Delivery

Transdermal drug delivery offers several important advantages over more traditional dosage forms.

- The steady permeation of drug across the skin allows for more consistent serum drug levels, often a goal of therapy. Intravenous infusion also achieves consistent plasma levels, but it is more invasive than transdermal drug delivery.
- The lack of peaks in plasma concentration can reduce the risk of side effects. Thus, drugs that require relatively consistent plasma levels are very good candidates for transdermal drug delivery.
- If toxicity were to develop from a drug administered transdermally, the effects could be limited by removing the patch.
- Another advantage is convenience, especially notable in patches that require only once weekly application. Such a simple dosing regimen can aid in patient adherence to drug therapy.
- Transdermal drug delivery can be used as an alternative route of administration to accommodate patients who cannot tolerate oral dosage forms. It is of great advantage in patients who are nauseated or unconscious.
- Drugs that cause gastrointestinal upset can be good candidates for transdermal delivery because this method avoids direct effects on the stomach and intestine. [21]

The ideal properties of transdermal delivery system are indicated in Table 4.

Disadvantages of Transdermal Drug Delivery

This is mainly due to inherent limitations of the TDDS listed below one of the greatest disadvantages to transdermal drug delivery

- Local irritation will develop at the site of application. Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation. For most patients, site rotation can minimize irritation. However, some patients develop severe allergic reactions to transdermal patches, and, in these cases, therapy must be discontinued.
- Another significant disadvantage of transdermal drug delivery is that the skin's low permeability limits the number of drugs that can be delivered in this manner. Because the skin serves protective functions, it inhibits compounds from crossing it. Many drugs with a hydrophilic structure permeate the skin too slowly to be of therapeutic benefit. Drugs with a lipophillic character, however, are better suited for transdermal delivery. [22]
- In order to maintain consistent release rates, transdermal patches contain a surplus of active molecule. A stable concentration gradient is the mechanism used to maintain consistent release rates and constant serum drug levels.
- Most transdermal patches contain 20 times the amount of drug that will be absorbed during the time of application. Thus, after removal, most patches contain at least 95% of the total amount of drug initially in the patch.
- Damage to a transdermal patch, particularly a membrane or reservoir patch, can result in poor control over the release rate. The release rate from a damaged patch would more likely be controlled by the skin than the patch, resulting in a higher, perhaps toxic, rate of drug delivery. Patients should be advised to discard a patch if the outer packaging or the patch itself appears damaged or altered in any way. [23]

4. Transdermal patch

A transdermal patch is a medicated adhesive patch that is placed on the skin to deliver a specific dose of medication through the skin and into the bloodstream. Often, this promotes healing to an injured area of the body. An advantage of a transdermal drug delivery route over other types of medication delivery such as oral, topical, intravenous, intramuscular, etc. is that the patch provides a controlled release of the medication into the patient, usually through either a porous membrane covering a reservoir of medication or through body heat melting thin layers of medication embedded in the adhesive. The main disadvantage to transdermal delivery systems stems from the fact that the skin is a very effective barrier; as a result, only medications whose molecules are small enough to penetrate the skin can be delivered in this method. Various transdermal dosage forms are indicated in Table 5. A wide variety of pharmaceuticals are now available in transdermal patch form. [24]

Components

The main components to a transdermal patch are:

- Liner - Protects the patch during storage. The liner is removed prior to use.
- Drug: Drug solution in direct contact with release liner.
- Adhesive - Serves to adhere the components of the patch together along with adhering the patch to the skin.

- Membrane - Controls the release of the drug from the reservoir and multi-layer patches
- Backing - Protects the patch from the outer environment.
- The components of transdermal patch are shown in Fig. 4.

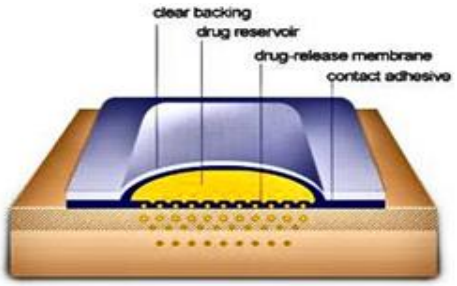

Figure 4: Components of transdermal patch

Types

Sample transdermal patches. On left is a 'reservoir' type, on the right a 'Single-layer Drug-in-Adhesive' version. Both contain exactly the same level of the same active ingredient with identical release rates. There are five main types of transdermal patches. [25]

Single-layer Drug-in-Adhesive

The adhesive layer of this system also contains the drug. In this type of patch the adhesive layer not only serves to adhere the various layers together, along with the entire system to the skin, but is also responsible for the releasing of the drug. The adhesive layer is surrounded by a temporary liner and a backing.

Multi-layer Drug-in-Adhesive

The multi-layer drug-in adhesive patch is similar to the single-layer system in that both adhesive layers are also responsible for the releasing of the drug. One of the layers is for immediate release of the drug and other layer is for control release of drug from the reservoir. The multi-layer system is different however that it adds another layer of drug-in-adhesive, usually separated by a membrane (but not in all cases). This patch also has a temporary liner-layer and a permanent backing.

Reservoir

Unlike the Single-layer and Multi-layer Drug-in-adhesive systems the reservoir transdermal system has a separate drug layer. The drug layer is a liquid compartment containing a drug solution or suspension separated by the adhesive layer. This patch is also backed by the backing layer. In this type of system the rate of release is zero order.

Matrix

The Matrix system has a drug layer of a semisolid matrix containing a drug solution or suspension. The adhesive layer in this patch surrounds the drug layer partially overlaying it Also known as a monolithic device.

Vapour Patch

In this type of patch the adhesive layer not only serves to adhere the various layers together but also to release vapour. The vapour patches are new on the market and they release essential oils for up to 6 hours. The vapours patches release essential oils and are used in cases of decongestion mainly. Other vapour patches on the market are controller vapour patches that improve the quality of sleep. Vapour patches that reduce the quantity of cigarettes that one smokes in a month are also available on the market.

Table 1: Criteria for selection of drugs for CDDS

Criteria	Pharmacological class	Non-peptide drugs	Peptide drugs
Drugs used for local effects in colon against GIT diseases	Anti-inflammatory drugs	Oxyprenolol, Metoprolol, Nifedipine	Amylin, Antisense oligonucleotide
Drugs poorly absorbed from upper GIT Drugs for colon cancer Drugs that degrade in stomach and small intestine	Antihypertensive antianginal drugs Antineoplastic drugs Peptides and proteins	Theophylline Pseudoephedrine Bromophenaramine,5-Flourouracil, Doxorubicin Bleomycin, Nicotine Ibuprofen, Isosorbides	Cyclosporine, Desmopressin Epoetin, Glucagon Gonadoreline, Insulin, Interferons Protirelin, sermorelin,
Drugs that undergo extensive first pass metabolism	Nitroglycerin corticosteroids	Prednisolone, hydrocortisone,	Saloatonin
Drugs for targeting	Antiarthritic, antiasthamatic drugs	5-Amino-salicylic acid	Somatropin, Urotoilitin

Table 2: Marketed products of pH dependent system

Trade Name	Formulation
Mesalamine Asacol	Eudragit S coated tablet
Mesalamine Salofac	Eudragit L coated tablet
Mesalamine Claversal	Eudragit L coated tablet
Budesonide Entocort	Eudragit L coated beads

Table 3: Marketed products of osmotic systems

Marketed product	Product name	Active Design	Dose
Acutrim	Phenylpropanolamine	Elementary pump	75 mg

Alpress LP	Prazosin	Push-Pull	2.5-5 mg
Covera HS	Verapamil	Push-Pull with time delay	180, 240 mg
Ditropan CR	Oxybutinin chloride	Push-Pull	5, 10 mg
Dynacire CR	Isradipine	Elementary pump	5, 10 mg
Efidac 24	Pseudoephiderine	Elementary pump	60 mg
Glucotrol	Glipizide	Push-Pull	5, 10 mg
Volmax	Salbutamol	Elementary pump	4, 8 mg

Table 4: Ideal Properties of a Transdermal Drug Delivery System

Properties	Comments
Shelf life	Up to 2 years
Patch size	< 40 cm2
Dose frequency	Once a daily to once a week
Aesthetic appeal	Clear, tan or white color
Packaging	Easy removal of release liner and minimum number of steps required to apply
Skin reaction	Non irritating and nonsensitizing
Release	Consistent pharmacokinetic and pharmacodynamic profiles over time

Table 5: Transdermal dosage form and Drug Indication Product Name Marketing Company

Drug	Drug indication /product name	Marketing Company
Scopolamine	Motion sickness/ Transderm-Scop	Novartis Consumer Health (Parsippany, NJ)
Nitroglycerin	Angina pectoris/ Transderm-Nitro	Novartis (East Hannover, NJ)
Clonidine	Hypertension Catapres-TTS	Boehringer Ingelheim (Ridgefield, CT)
Estradiol	Menopausal symptoms Estraderm	Novartis (East Hannover, NJ)
Fentanyl	Chronic pain/ Duragesic	Janssen Pharmaceutica (Titusville, NJ)
Nicotine	Smoking cessation /Nicoderm	Pro Step GlaxoSmithKline (Philadelphia, PA)
Testosterone	Deficiency/Testoderm Alza	Mountain View, CA
Lidocaine/epinephrine	Local dermal analgesia/ Iontocaine	Iomed (Salt Lake City, UT)
Estradiol/norethidrone	Menopausal symptoms /Combipatch	Novartis (East Hannover, NJ)
Lidocaine	Post-herpetic neuralgia pain/ Lidoderm	Endo Pharmaceuticals (Chadds Ford, PA)
Ethinylestradiol	Contraception Ortho/ Evra Ortho	Ortho-McNeil Pharmaceutical (Raritan, NJ)
Estradiol	Menopausal symptoms/ Climara pro	Pro Bayer Healthcare Pharmaceuticals

5. Conclusion

CDDS offers considerable therapeutic benefits to patients in terms of both local and systemic treatment. Colon specificity is more likely to be achieved with systems that utilize natural materials that are degraded by colonic bacterial enzymes. All the approaches of colon drug delivery provide means for treatment of local diseases associated with the colon or for systemic absorption of poorly absorbable drugs. The foregoing shows that TDDS have great potentials, being able to use for both hydrophobic and hydrophilic active substance into promising deliverable drugs.

6. References

[1] AK Philip, B Philip. Colon Targeted Drug Delivery Systems: A Review on Primary and Novel Approaches. Oman med. J, 2010, 25(2): 79-87.

[2] WN Charman, HK Chan, BC Finnin, SA Charman. Drug Delivery: A Key Factor in Realising the Full Therapeutic Potential of Drugs. Drug Development Research, 1999, 46: 316-27.

[3] JT Santini Jr, AC Richards, R Scheidt, MJ Cima, R Langer. Microchips as Controlled Drug-Delivery Devices. Angew. Chem. Int. Ed., 2000, 39: 2396-407.

[4] J Kopecek. Smart and genetically engineered biomaterials and drug delivery systems. European Journal of Pharmaceutical Sciences, 2003, 20, 1-16.

[5] N Patel, J Patel, T Gandhi, T Soni, S Shah. Novel pharmaceutical approaches for colon-specific drug delivery: An overview. J. Pharm. Res., 2008, 1(1): 2-10.

[6] KS Pawar, SP Pawar, VA Patel. Microbial polysaccharidases in colon specific drug delivery. Int. J. Pharm. Sci. Rev. Res., 2011, 6(2): 188-96.

[7] SR Naikwade, PP Kulkarni, SR Jathar, AN Bajaj. Development of time and pH dependent controlled release colon specific delivery of tinidazole. Daru, 2008, 16(3): 119-127.

[8] JW Fara. Novel Drug Delivery and its Therapeutic Application. In: Presscot LF, Nimmo WS, editors.

Colonic drug absorption and metabolism. Wiley: Chichester, 1989: 103-120.

[9] M Mackay, E Tomlinson. Colonic delivery of therapeutic peptides and proteins, In: Biek PR, editors. Colonic drug absorption and metabolism. New York: Marcel Dekker, 1993: 159-176.

[10] DR Friend, GW Chang. A colon-specific drug delivery system based on drug glycosides and glycosidase of colonic bacteria. J Med Chem, 1984, 27: 261- 266.

[11] DF Evans, G Pye, R Bramley, AG Clark, TJ Dyson, JD Hardcastle. Measurement of gastrointestinal pH profiles in normal ambulant human subjects. Gut, 1988, 29: 1035-1041.

[12] T Bussemer, I Otto, R Bodmeier. Pulsatile drug-delivery systems. Crit Rev Ther Drug Carr Sys, 2001, 18: 433-458.

[13] M Ashord, JT Fell, D Attwood, H Sharma, P Woodhead. An evaluation of pectin as a carrier for drug targeting to the colon. J Control Rel, 1993, 26: 213- 220.

[14] E Fukui, N Miyamura, M Kobayashi. An in vitro investigation of the suitability of presscoated tablets with hydroxypropylmethylcellulose acetate succinate (HPMCAS) and hydrophobicn additives in the outer shell for colon targeting. J Control Rel, 2000, 70: 97-107.

[15] M Vassallo, M Camilleri, SF Phillip, ML Brow, NJ Chapman, GM Thomforde. Transit through the proximal colon influences stool weight in the a irritable bowel syndrome. Gastroenterology, 1992, 102: 102-108.

[16] MR Vonderohe, M Camolleri, LK Kvols, GM Thomforde. Motor dysfunction of the small bowel and colon in patients with the carcinoid syndrome and diarrhea. New Eng J Med, 1993, 329: 1073-1078.

[17] T Takaya, K Niwa, M Muraoka, I Ogita, N Nagai, R Yano, G Kimura, Y Yoshikawa, H Yoshikawa, K Takada. Importance of dissolution process on systemic availability of drugs delivered by colon delivery system. J Control Rel, 1998, 50(1-3): 111-122.

[18] M Muraoka, Z Hu, T Shimokawa, S Sekino, R Kurogoshi, Y Kuboi, Y Yoshikawa, K Takada. Evaluation of intestinal pressure-controlled colon delivery capsule containing caffeine as a model drug in human volunteers. J Control Rel, 1998, 52(1-2): 119-129.

[19] DJ Hay, H Sharma, MH Irving. Spread of steroid containing foam after intrarectal administration. Brit Med J., 1979, 1: 1751-1753.

[20] S Watanabe, H Kawai, M Katsuma, M Fukui. Colon specific drug release system. U.S. Patent, 1998, 09/183339.

[21] E Keleb, RK Sharma, B MosaEsmaeil, AZ Abdalkadar. Review on Transdermal Drug Delivery System- Design and Evaluation, International Journal of Advances in Pharmaceutical Sciences, 2010, 1(15): 201-211.

[22] A Arunachalam, M Karthikeyan, VD Kumar, M Prathap, S Sethuraman, S Ashutosh Kumar, S Manidipa. Transdermal Drug Delivery System: A Review, Current Pharma Research, 2010, 1(1): 70-81.

[23] GM Shingade, Q Amer, PM Sabale, ND Gramprohit, MV Gadhave, SL Jadhav, DD Gaikwad . Review on: recent trend on transdermal drug delivery system, Journal of Drug Delivery & Therapeutics, 2012, 2 (1): 66-75.

[24] D Patel, A Sunita, B Parmar, N Bhura. Transdermal Drug Delivery System: A Review. The Pharma Innovation, 2012, 1(4): 66-75.

[25] SK Vishwakarma, SK Niranjan, R Irchhaiya, N Kumar, A Akhtar. A Novel transdermal drug delivery system, International Journal of research of pharmacy, 2012, 3(8): 39-44.

[26] P Sakalle, S Dwivedi, A Dwivedi. Design, Evaluation, Parameters and Marketed Products of transdermal patches: A Review. Journal of Pharmacy Research, 2010, 3(2): 235-240.