ISSN: 2320 - 4230

Journal of Drug Discovery and Therapeutics
Available Online at www.jddt.in
CODEN: - JDDTBP (Source: - American Chemical Society)
Volume 8, Issue 12, December: 2020, 01-05

Research Article

COLON TARGETED DRUG DELIVERY SYSTEM FOR DICLOFENAC DRUG

Makwana Rajeshree P*[1]. Dr. Kinjal H Shah [1]

[1]Department of Pharmaceutics, B.Pharmacy College Rampura, Godhra, Gujarat, India

Corresponding Author**: Makwana Rajeshree P**

Disclosure statement: Nil

Abstract:
The colon targeted drug delivery has a number of important implications in the field of pharmacotherapy. Oral colon targeted drug delivery systems have recently gained importance for delivering a variety of therapeutic agents for both local and systemic administration. Targeting of drugs to the colon via oral administration protect the drug from degradation or release in the stomach and small intestine. It also ensures abrupt or controlled release of the drug in the proximal colon. Various drug delivery systems have been designed that deliver the drug quantitatively to the colon and then trigger the release of drug. This review will cover different types of polymers which can be used in formulation of colon targeted drug delivery systems. Microspheres were prepared. The size range of the microsphere was 211 to 500 µm while drug content was between 70.40 and 91.50 % depending on the polymer used and the polymer ratio. It has good flow properties, while angle of repose was < 49°, indicating free-flowing properties. The microspheres were spherical in shape with smooth and nonporous surface, polymers gave better sustained release (F5) than the others. Microspheres prepared with drug: EC: PAP show the highest drug content, possess good flow properties and surface morphology, as well as promising drug release for colon specific drug delivery of diclofenac sodium for possible treatment of colon disease.

Keywords: Diclofenac, colon targeted delivery, controlled delivery, Ethyl cellulose

INTRODUCTION

Colon specific drug delivery systems are designed to permit targeted drug release to the terminal ileum & proximal colon. This delivery system, by means of combination of one or more controlled release mechanisms, hardly releases drug in the upper part of the gastrointestinal (GI) tract, but rapidly releases drug in the colon following oral administration.[1] In view of CDDS specifically delivering drug to the colon, a lot of benefits would be acquired in terms of improving safety and reducing toxicity when treating local or systemic chronic diseases. First, as for treating localized colonic diseases, *i.e.* ulcerative colitis, Crohn's disease and constipation *etc*., the optimal drug delivery system, such as CDDS, while increased considerably in the colon, resulting in alleviated GI side effects. [2] To our knowledge, CDDS could provide reliable protection against GI enzymatic degradation by releasing the polypeptide and protein nearly unchanged and fully efficacious in the preferred colon, thereafter resulting in remarkably increased bioavailability for protein and polypeptide. Finally, CDDS would be advantageous when a delay in absorption is desirable from a therapeutical point of view, as for the treatment of diseases that have peak symptoms in the early morning and that exhibit circadian rhythms. [3]

There were currently a few strategies to achieve colonic specificity. The aim of this study was to explore the feasibility of the time- and pH-dependent CDDS, diclofenac sodium (DS) and 5-aminosalicylic acid (5-ASA) being selected as model drugs, respectively. Besides, we were intended to exploit the typical pharmaceutical coating technology to attain the time-and pH-dependent colon-specific drug delivery. [3-5] Time-dependent colon-specific DS coated tablets consisted of a tablet core and a coating layer composed of a water-insoluble ethylcellulose (EC) and a water-soluble channeling agent. pH-dependent colon-specific 5-ASA coated pellets consisted of a pellet core and a coating layer of the pH-sensitive methacrylic acid copolymers. [6]

The most commonly used pH-dependent polymers are derivatives of acrylic acid and cellulose. The pH dependent polymers used in colon specific drug delivery are insoluble at low pH levels but become increasingly soluble as pH rises. e.g., Eudragit and shellac. Microparticles are a type of drug delivery systems where the particle size ranges from one micron to few mm. [7] Microspheres are characteristically free flowing powders consisting of proteins and synthetic polymers,

biodegradable in nature and having a particle size less than 200 µm (normally the range is also acceptable up to 1000 – 1500 µm) [10]. Dicolofenac sodium (DS) is a well-known nonsteroidal anti-inflammatory drug (NSAID). It is well absorbed in the colon, and colon specific release can be used for the treatment of various diseases like colorectal cancer and inflammatory bowel diseases. [8,9]

To deliver the compounds in non degraded form to lower part of the Gastrointestinal Tract (GIT), they must first of all pass through the stomach, the upper part of intestine and must use the characteristics of the colon to specifically release the drugs in this part of digestive tract.Various approaches have been developed for colon targeting including pH dependent systems, Time dependent system and Microbially triggered delivery system. [10]

In addition, drug delivery to the colon is also advantageous from the view point of circadian biorhythms since it can be provide a noctumal release of drugs for diseases that are characterized by night time or early morning onset.Currently, four strategies are being pursued to achieve colon specific drug delivery. [11-16]

MATERIALS:

Diclofenac sodium received as gift sample, Ethyl cellulose, Polyvinyl alcohol

METHOD OF PREPARATION:

The microspheres of diclofenac sodium were prepared by solvent evaporation technique using ethyl cellulose. Polyvinyl alcohol (1%w/v), Span 60, Methylene chloride, Gelatin amount gelatin & drug (Diclofenac sodium) was dissolved in sufficient water (5 ml). 200 mg ethyl cellulose & span 60 was dissolved in 2 ml of methyl chloride. Now the aqueous phase was dispersed into the organic phase, it gives water in oil emulsion.Then this emulsion was emulsified in 100 ml of a 1% w/v PVA aqueous solution. Emulsion was maintained under agitation for 20 mins & than for 2hrs to allow evaporation of solvent. Microspheres were collected, rinsed with water & dry. During the 5 h stirring period, alcohol was completely removed by evaporation. after which the microcapsules were separated by filtration. The microcapsules were kept for 12 h at room temperature for drying and stored in desiccators for complete removal of moisture.

Table 1: Composition of colon specific microspheres of diclofenac sodium

Ingredients	Quantity to be taken					
	F1	F2	F3	F4	F5	F6
Diclofenac sodium					0.500 gm	
Ethyl cellulose	0.100 gm	0.100 gm	0.200 gm	0.100 gm	0.200 gm	0.100 gm
PVA (1%w/v)	10ml	20ml	40ml	80ml	100 ml	120ml
Span 60	0.100 gm	0.120 gm	0.140 gm	0.180 gm	0.200 gm	0.220 gm
Methylene chloride	2 ml	1ml	2 ml	1 ml	2 ml	2 ml
Gelatin	1 gm	2 gm	1 gm	2 gm	2 gm	2 gm

Evaluation:

1. **Characterization of drug:** Characterisation of drug was done by determining the solubility, melting point using capillary method and comparing the IR spectra of obtained drug with standard spectrum using FTIR spectroscopy.

2. **Drug-excipient compatibility study:** The drug-Excipient interaction study was carried out by physical observation and FTIR spectroscopy.

3. **Particle size**: Using optical microscopy method particle size of the formulations was determined. Bulk density, tapping density, compressibility index and angle of repose were evaluated. At least 100 microspheres were analyzed for each formulation and the mean particle size was calculated.

4. **SEM**: Particle size of the formulations was determined by scanning elecron microscopy.

5. **Determination of uniformity of drug content:** 20 tablets were weighed and powdered by using pestle mortar. An amount equivalent to 50 mg was shaken with 100 ml methanol and sonicated for 10 minute. The solution was filtered through Whatman filter paper and the content of DS was determined by measuring absorbance at 275 nm on double beam UV spectrophotometer after suitable dilution.

6. ***In vitro* drug release study:** All batches F1–F6 were further evaluated for *in vitro* drug release study. *in vitro* drug release study was carried out using USP apparatus II (Paddle) and the medium was 0.1N HCl (pH 1.2) and phosphate buffer pH 6.8. The quantity of

dissolution medium was 900 ml. The speed of paddle was 50 rpm and temperature of dissolution medium was 37±0.5 ºC. Dissolution study was carried out in 0.1 N HCl for 2 hrs and then placed in phosphate buffer (pH 6.8) until complete release of the drug. Five ml aliquots were withdrawn at fix intervals and replacement was made each time with five ml of fresh dissolution medium to maintain sink condition. Every time withdrawn sample was filtered through Whatman filter paper and analyzed drug content at 275 nm using UV-visible spectrophotometer *in vitro* drug release study for each sample was done in triplicate.

7. **Stability study:** The stability studies were carried out for the optimized formulation. The samples were stored at 40±2 ^{0}C and 75±5 %RH for three month to access their stability. The protocol of stability studies was in compliance with ICH guidelines for stability testing intended for the global market. After every 30 days the samples were withdrawn and characterized for hardness, friability, drug content and in-vitro drug release study.

RESULTS:

In the present work, the colon specific microspheres of diclofenac sodium were prepared using solvent evaporation method. For the colon targeting synthetic polymers namely ethyl cellulose (EC), Poly Vinyl Alohol (PVA), were used to prepare the microspheres. The prepared formulations of different drug polymer ratio were evaluated for physical properties like particle size, bulk density, tap density, angle of repose and percent drug encapsulation efficiency and in vitro drug release study.

1. Characterization of drug: Determination by Uv spectroscopic method and other morphological charcterisic.

Solubility: Soluble in hot water, forming a viscous solution; practically insoluble in chloroform, Acetone, Methanol Also polymer swells in 0.1 N HCl and phosphate buffer and shows good gelling properties.

2. Drug-excipient compatibility study: No interation measured by Infra red and Dsc study

3. Particle size: Microscopic parameters (Table 2) such as bulk density, tapping density, compressibility index and angle of repose were evaluated, which provide the basis for optimization of the flow property of microspheres. All the microspheres of various formulations showed good flow property with an angle of repose less than 49^o.

Table 2: Microspheres of diclofenac sodium (mean ± SD, n = 3)

Formulation	Particle size (µm)	Drug content (%)	Angle of repose (o)
F1	302 µm±2.5	53.39±0.236	36.9±0.7865
F2	279 µm ±3.0	76.89±0.236	31.6±0.6754
F3	452 µm±2.8	62.62±0.236	35.9±0.7654
F4	211 µm±1.5	80.70±0.236	33.5±0.1256
F5	399 µm ±3.0	92.52±0.236	27.2±0.8139
F6	500 µm ±3.2	70.87±0.236	34.0±0.1152

4. SEM: Scanning electron microscopy reveals that F1, F2, F3, F4, F5 and F6 formulation produced spherical microspheres as compared to F3 formulation. The microspheres of F4 formulation were of irregular shape with large pores and smooth surface. In the formulation F5 (prepared with EC, PVA & Span 60), the microspheres were of smoothest surface (as compared to others) without any pore formation (Fig. 1). Scanning electron microscopy confirmed that the microspheres were the spherical shaped with very rough surface while microspheres of F1, F2 and F4 .

Fig 1: SEM photograph of microsphere batch F5 formulations

5. Determination of uniformity of drug content: All the formulation selection for uniformity test was uiform found. Drug content in almost formulation determine. It is very good characteristic for formulation of uniformity drug content.

6. In vitro drug release: In vitro drug release studies of all the formulations were performed in pH 6.8 phosphate buffer at 276 nm. Drug release from the formulation varied significantly among the different polymers as well as their combination and ratio in the formulations. The drug release at the end of 12 h was 69.3, 60.82, 72.52, 88.9, 82.6, and 92.23 % for formulation F1, F2, F3, F4, F5 and F6 respectively. Formulation F1 (followed by F3) containing ethyl cellulose showed the maximum release while the formulation F2 showed the minimum release after the 12 h.

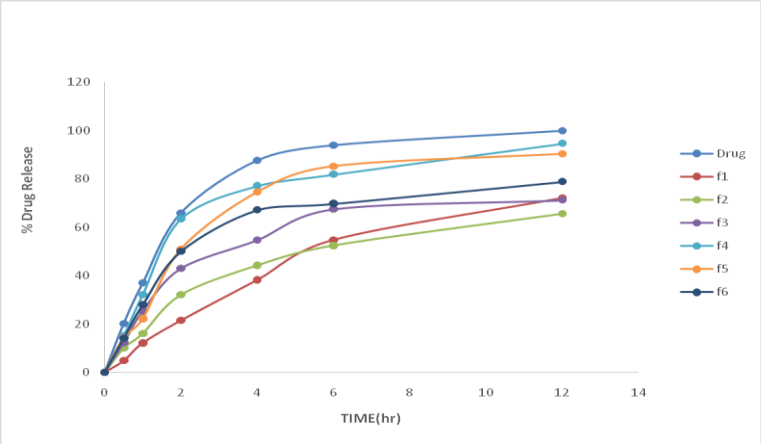

Fig 2: In vitro drug release study of colon specific microspheres of diclofenac sodium

DISCUSSION:

All the prepared formulations showed good percent drug loading. The highest percent drug content of Formulation F5. Delivering diclofenac with the colon targeting not only provides the high concentration in the colon region (where it is required at high dose in colorectal disease but also helps to avoid the possible gastric irritation. SEM study showed spherical shaped particles with rough and porous surface (except that of formulation F6 which was prepared with EC, PVA & Span 60). The drug release was very less in first 2 h and when the drug was exposed to the medium mimicking the colon, the drug release was found to be increasing abruptly. This lag time in drug release ensured the delivery of the maximum amount of drug in the colonic pH and colonic environment. The in vitro drug release study indicated that the combination of polymer and their changed ratio changed the release rate of drug from microspheres. The F6 formulation containing ethyl cellulose showed maximum release and F5 formulation containing CAP showed slow release than F1 at the same ratio of polymer. The ethyl cellulose formed the very rough surface (as confirmed by SEM) of the microspheres through which drug release was maximum by dissolving the layers of rough surface of polymer. The formulation F3 showed biphasic pattern i.e. initial fast release (as above 50 % in only ½ h) called as burst effect, due to the large size of pores on the surface of microspheres and then sustained release due to smooth surface. The formulation F4 showed the second highest drug release after F1. This might be due to decrease in the concentration of EC. But the F5 formulation has very smooth surface and good flow property as well as good drug release.

CONCLUSION:

Colon specific microspheres of diclofenac sodium using EC, PVA and Span 60 have been successfully prepared. Formulation F5 (prepared with drug: EC: PVA ratio) is the optimized preparation and demonstrate potentially suitable drug release for the colonspecific delivery of diclofenac.

REFERENCES:

1. Patel M, Amin AF. Process optimization and characterization of mebeverine hydrochloride loaded guar gum microspheres for irritable bowel syndrome. Carbohydrate Polymers. 2011; 86 (2): 536–545.
2. Friend DR. Issues in oral administration of locally acting glucocorticosteroids for treatment of inflammatory bowel disease. Aliment Pharmacol Ther, 1998; 12 (7): 591-603.

3. Basit A, Bloor J. Perspectives on colonic drug delivery, Business briefing. Pharmtech 2003; 185-190.

4. Chaurasia M, Chourasia MK, Jain NK, Jain A, Soni V, Gupta Y, Jain SK. Cross- linked guar gum microspheres, A viable approach for improved delivery of anticancer drugs for the treatment of colorectal cancer. AAPS PharmSciTech 2006; 7(3): Article 74.

5. Ciftci, K. Alternative approaches to the treatment of colon cancer. Eur. J. Pharm. Biopharm. 1996; 42: 160–170.

6. Watts P, Illum L. Colonic drug delivery. Drug Dev Ind Pharm 1997; 23: 893-913.

7. Smalley W, Ray WA, Daugherty J, Griffin MR. Use of nonsteroidal anti-inflammatory drugs and incidences of colorectal cancer. Arch Intern Med. 1999; 159: 161–166.

8. Philip AK, Philip B. Colon targeted drug delivery systems: a review on primary and novel approaches. Oman Med J. 2010; 25: 70-78.

9. Nath B, Nath LK, Mazumdar B. Design and development of Metformin HCl floating microcapsules using two polymers of different permeability characteristics. Int. J. Pharm. Sci. Nanotech. 2009; 2: 177-186

10. Semalty A, Semalty M, Singh D, Rawat MSM, Development and physicochemical evaluation of pharmacosomes of diclofenac, Acta Pharm. 2009; 59: 335–344.

11. Shabaraya A, Narayanachrayulu R. Design and evaluation of chitosan microspheres of metoprolol tartrate for sustained release. Indian J. Pharm. Sci. 2003; 65: 250-252.

12. Jain A, Sing V, Gupta Y, Jain SK, Perspectives of biodegradable natural polysaccharides for sitespecific drug delivery to the colon. J Pharm Pharmaceut Sci. 2007; 10 (1): 86-128.

13. Collet JP, Sharpe C, Belzile E, Boivin, J.F. Abenhaim, L. Colorectal cancer prevention by non-steroidal antiinflammatory drugs: effects of dosage and timing. Br. J. Cancer 1999; 81: 62–68.

14. Langman MJ, Cheng KK, Gilman EA, Lancashire RJ. Effect of anti-inflammatory drugs on overall risk of common cancer: case-control study in general practice research database. BMJ 2000; 320: 1642– 1646.

15. Ilyas M, Straub J, Tomlinson IP, Bodmer WF. Genetic pathways in colorectal and other cancers. Eur J Cancer. 1999; 35 (14): 1986-2002.

16. Yoshida T, Lai TC, Kwon GS, Sako K. pH- and ionsensitive polymers for drug delivery. Expert Opin Drug Deliv. 2013; 10(11): 1497-513.