RESEARCH ARTICLE

STUDIES ON DEVELOPMENT OF NOVEL COMBINED TIME AND pH-DEPENDENT SOLVENTLESS COMPRESSION COATED DELIVERY SYSTEMS FOR COLONIC DELIVERY OF DICLOFENAC SODIUM

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Abstract: Solventless compression coating was one of the strategies for delivering drugs to the colon based on gastrointestinal pH and transit time concept. The present study was aimed to develop rapidly disintegrating diclofenac sodium core tablets compression-coated with a mixture of time dependent hydrophilic swellable polymer hydropropylmethylcellulose (HPMC) and pH responsive soluble polymer Eudragit® S 100 (ED) in different ratios. The effect of proportion of HPMC and ED in the coat on premature drug release in upper part (stomach and small intestine) of gastrointestinal tract and the amount of drug release in colon target area was studied. It was found that core tablets compression-coated with HPMC and ED alone fails to prevent drug release in upper part of gastrointestinal tract and release was incomplete in the colon target area from HPMC compression-coated tablets, where as drug release was not sustained in colon from ED compression-coated tablets. The formulations released 1.24% to 6.82% of drug in physiological environment of stomach and small intestine depending upon proportion of HPMC and ED in the coat. The core tablets compression-coated with HPMC and ED mixture in the ratio 6:4 was found to be suitable for targeting diclofenac sodium to the colon owing to its minimal drug release in physiological environment of stomach and small intestine and releases 92% of drug in the target area. The presence of ED in hydrophilic compression coat retarded the initial swelling of the coat in acidic to weakly acidic pH, but in alkaline pH, enhancement in drug release rate was observed due to the dissolution of ED from the coat with time resulting in a porous coat structure, resulted in a faster and controlled drug release in the target area.

Keywords: Diclofenac sodium, HPMC, eudragit® S 100, solventless compression coating.

INTRODUCTION

Dicolofenac sodium (DS) is a well known representative of non-steroidal anti-inflammatory drugs (NSAID's) widely used to control pain and inflammation of rheumatic and non-rheumatic origin [1]. NSAIDs also exert preventive effect against colon cancer that seems to be due to increased colon cell apoptosis [2]. The conventional DS tablets make the drug immediately available for absorption in upper gastrointestinal tract resulting local GI toxicity varying from minor gastric discomfort to ulceration and bleeding of the mucosa [3]. It is well documented that the GI toxicity is not only caused by the inhibition of the prostaglandin synthesis, but is probably also due to direct contact of the drug with the mucosa [4]. In addition rapid systemic clearance of this drug, repeated daily dosing of 3 to 4 times is required in maintainance therapy that influence patient compliance. Colon targeted controlled release formulation are thus warranted to promote patient compliance and to reduce upper GI toxicity to some extent. DS was selected as a model drug since it is well absorbed in the colon [5] and thus a formulation of DS with negligible to no drug release in upper part of GI tract and controlled release in colonic region would achieve effective therapeutic concentration of drug locally in colon. At the same time, such a formulation would minimize systemic or upper GI tract side effects and colon specific release can be used for the treatment of widespread inflammatory bowel diseases.

Colon-specific drug delivery systems (CDDS) were developed to reduce side effects and achieve high local drug concentration at the afflicted site in the colon, hence optimal therapeutic effectiveness and good patient compliance [6-8]. It has been proved effective in treating colonic diseases such as inflammatory bowel diseases and colon cancer or improving absorption of protein or polypeptide drugs [9, 10]. A colonic drug delivery system is expected to protect the drug during the transit time in the gastrointestine and to allow its release only in the colon. The various approaches that have been studied for targeting orally administered drugs to the colon include use of pH-sensitive polymers [10, 11], time-dependent dosage forms [12, 13] and the use of carriers degraded by enzymes produced by colonic bacteria [14, 15].

Complicated by physiological variation in gastrointestinal conditions, many CDDS designs reported in literature have problems. The goal of CDDS design is to cut off precolon drug release and release drug at the afflicted site. Among the strategies, compression coated systems seem to be superior in preventing premature drug release in stomach and small intestine, while beginning to release the active agents at the proximal colon. On the other hand, the compression coated systems, usually in tablet form, is convenient to manufacture, and no special coating solvents or coating equipments are needed for coating process. The coating material of compression–coated systems can either be microbially degradable or not. Polysaccharides, such as guar gum and pectin, have been evaluated for colonic drug delivery as a compression coating material both in vitro and in vivo. However, because of high hydrophilicity of polysaccharide, the polysaccharides coating may be soaked by water within a short time, and great thickness is needed for tight control on precolon release [9]. It is reported that pectin USP was the correct choice among the other pectin grades for compression coating around core tablets, but a minimum coat weight of 700mg would be required for a dosage form to reach the colon [14]. Studies with guar gum as compression coating showed that even without the action of specific enzymes or caecal content, drugs begin to leak out shortly after immersion in water, and no obvious release lag time was observed [15]. Another draw back of polysaccharide compression coated systems is their deficiency in strength after swelling in aqueous media, which may render them susceptible to tearing force generated by gastrointestinal movement. To overcome this problem, HPMC has been tested to hybridize with pectin to strengthen the so-formed gel [16].

In the present study, diclofenac sodium core tablets were compression-coated with a mixture of Hydroxypropylmethylcellulose and eudragid S 100 in different ratios for colon–specific delivery. The effect of formulation variables on the two critical release properties, drug release in physiological environment of stomach and, small intestine and drug release in target area / colon was investigated.

MATERIALS AND METHODS

Materials

Diclofenac sodium was obtained as a generous gift sample from Emcure Pharmaceuticals Ltd. Pune, India. pH sensitive methacrylic acid co-polymer Eudragit® S 100 was supplied as gift sample by Degussa India Pvt. Ltd., Mumbai. Hydroxypropylmethylcellulose K4M (HPMC) and Microcrystalline cellulose (Avicel pH 101) was purchased from Colorcon Asia, Goa, India. Crosslinked polyvinyl pyrolidone was a gift sample from M/s Arbindo Pharma Ltd., Hyderabad, India. Talc and magnesium stearate used for the preparation of tablets were purchased from Loba chemicals, Mumbai, India.

Preparation of rapidly disintegrating diclofenac sodium core tablets

Rapidly disintegrating diclofenac sodium core tablets (average weight 120mg) were prepared by direct compression technique from a powder mixture containing 100 mg of diclofenac sodium and 5 mg (5% weight of the drug) of a super disintegrant crosslinked polyvinyl pyrrolidone (Table 1). A weighed quantity of diclofenac sodium and crosslinked PVP for 50 tablets of each batch was mixed thoroughly with mortar and pestle and passed through a mesh (149 µm) to ensure complete mixing. The uniformity of mixing was assessed by conducting content uniformity test on the sample of powder mixture. Quantity weighing 120 mg was taken and compressed into tablets using 8 mm round, flat and plain punches on a single station tablet punching machine (Cadmach, India). The quality control tests such as weight variation, hardness (crushing strength), friability and dissolution were performed on the core tablets.

Table 1. Composition of rapidly disintegrating diclofenac sodium

Core Tablets	
Ingredients	**Quantity (mg) present in core formulation**
Diclofenac sodium	100
Crosslinked PVP	5
Spray dried lactose	11.4
Talc	2.4
Magnesium stearate	1.2
Total Weight (mg)	**120**

Physical characterization of core and compression coated tablets

The designed core and compression-coated tablet formulations were studied for their physical properties like weight variation, hardness, friability, and drug content uniformity. For estimating weight variation, 20 tablets of each formulation were weighed using a single pan electronic balance (Elico, Mumbai, India). The hardness of five tablets was measured using Monsanto tablet hardness tester. Friability was determined on 20 tablets in a Roche's friabilator for 4 min at 25 rpm. For estimation of drug content, ten tablets were crushed, and the aliquots of powder equivalent to 100 mg of drug was extracted in phosphate buffer pH 7.4 and analyzed spectrophotometricaly at 275nm.

***In vitro* drug release studies in artificial gastric and intestinal fluid**

The ability of the prepared compression coated tablets to prevent or to remain intact with respect to time in the physiological environment of stomach and small intestine in pH conditions prevailing in stomach and small intestine was assessed by *in vitro* drug release in USP XXIII dissolution rate test apparatus (apparatus type 1, 100rpm, 37±0.5 °C) for 2 h in pH 1.2 (900 ml), as the average gastric emptying time is 2 h..Then the dissolution media was replaced with pH 7.4 phosphate buffer (900ml) for rest of the experiment and was continued for another 22 h as the usual colon transit time is 20-30 h. At the end of the time periods 5 ml sample were taken and analyzed for percentage of drug release by UV spectrophotometer at 275 nm (Shimadzu, Japan).

RESULTS AND DISCUSSION

Dissolution of core tablets

Because outer hydroxypropylmethylcellulose coat function as the controlling mechanism of diclofenac sodium release from compression coated tablets, the core tablets were prepared with fast disintegration and dissolution characteristics. Tested in USP disintegration tester (Elico, India), the core tablets were found to disintegrate within 1min showing required fast disintegration characteristics. Because diclofenac sodium core tablets contains a super disintegrant cross PVP and water soluble directly compressible diluent spray dried lactose which might have contributed for such a fast disintegration of core tablets, over 90% of diclofenac sodium dissolved in pH 1.2 buffer within 40 min. The fast disintegrating and dissolution of the core tablet prevent it from being the rate limiting factor.

Preparation of diclofenac sodium compression-coated tablets

After confirming compliance with the above mentioned tests, the formulated core tablets were compression coated with the different coat formulation of HPMC:ED mixture (core: coat ratio 1:3) with a coat weight of 360 mg. The compression coat powder material was prepared using mixture of hydroxyl propyl methyl cellulose and eudragit® S 100 in different ratio (Table 2). The microcrystalline cellulose is added in the coat formulation as a direct compression aid. For compression coating about 45% of coat weight powder was first placed in the die cavity. Then, the core tablet was carefully positioned at the centre, which was then filled with the remainder of the coat powder material 55%. The coating material was then compressed around the core tablet by using 12 mm round plain punches. The compression coated diclofenac sodium tablets were then evaluated for drug content, hardness, friability and in vitro drug release characteristics.

Table 2. Composition of compression-coat powder material for diclofenac sodium core tablets

Ingredients	Quantity (mg) present in coat formulation						
	H100	**ED100**	**HED91**	**HED82**	**HED73**	**HED64**	**HED 55**
HPMC	300	-	270	240	210	180	150
ED	-	300	30	60	90	120	150
MCC	19.5	19.5	19.5	19.5	19.5	19.5	19.5
Talc	7	7	7	7	7	7	7
Mg St.	3.5	3.5	3.5	3.5	3.5	3.5	3.5
HPMC:ED	10:0	0:10	9:1	8:2	7:3	6:4	5:5
Total Wt (mg)	**330**	**330**	**330**	**330**	**330**	**330**	**330**

Physical characterization of diclofenac sodium core tablets

The rapidly disintegrating diclofenac sodium core tablets were prepared by direct compression technique using water soluble spray dried lactose as a direct compression aid. The compressional force was adjusted to give core tablets with approximately 3.1 kg/cm^2 hardness. The physical parameters for the core tablet formulations were within the limits. Average weight of the core tablet was fixed at the lowest possible level (120 mg) to accommodate maximum amount of coat material over the core tablet and the average percentage deviation of core was with in the official limit. The core tablet formulations passed the test for friability (<0.6%) and core tablets showed 98.20% of labeled amount of drug, indicating uniformity of drug content in the core tablet formulation (Table 3).

Physical characterization of diclofenac sodium compression-coated tablets

The compression-coated tablet formulations were prepared according to the formula given in Table 2. The compression-coated tablets of different formulations were subjected to various evaluation tests such as uniformity of weight, drug content, hardness, friability, and *in vitro* dissolution. In a weight variation test, the pharmacopoeial limit for the percentage deviation for the tablets of more than 250 mg is ± 5%. The average percentage deviation of all tablet formulations was found to be within the above limit, and hence all formulations passed the test for uniformity of weight as per official requirements. Good uniformity in drug content was found among different batches of the tablets, and the percent of drug content was in the range of 95.06% to 101.82%. All the formulation showed a high hardness value in the range of 4.8 to 5.3 kg/cm^2. Tablet hardness is not an absolute indicator of strength. Another measure of tablet's strength is friability. The compressed tablets that lose less than 1% of their weight are generally considered acceptable. In the present study, the percentage friability of all the batches formulation was below 1%, indicating that the friability is with in the limits.

Table 3. Physical characterization of diclofenac sodium core and compression-coated tablets

Formulation code	Weight (mg)	Hardness (Kg/cm^2)	Weight Variation (%)	Friability (%)	Drug Content (%)
Core	120	3.1	1.52	0.34	98.20
H100	452	4.9	3.52	0.56	96.14
ED100	450	5.2	2.40	0.56	98.00
HED91	451	5.3	2.21	0.28	99.10
HED82	454	5.2	2.00	0.32	98.20
HED73	450	5.2	2.86	0.32	97.25
HED64	453	5.3	2.21	0.48	98.99
HED55	453	5.3	2.20	0.12	101.82

All the compression-coated tablet formulations showed acceptable pharmacotechnical properties and complied with the in-house specification for weight variation, drug content, hardness and friability.

***In vitro* drug release studies**

The present investigation was aimed to develop novel oral colon targeted compression coated tablet systems of diclofenac sodium for safe and effective therapy of rheumatoid arthritis by using HPMC-ED mixture as a coating material. Hydroxypropylmethylcellulose and eudragit® S 100 proportion ratio are shown in Table 3. The ability of compression coated tablets of diclofenac sodium to remain intact in the physiological environment of stomach and small intestine was assessed by conducting *in vitro* drug release studies in 0.1N HCL for 2h and in phosphate buffer pH 7.4 for 3h and, continued in phosphate buffer pH 7.4 for another 19 h to assess the ability of the compression coated tablets to release drug in the physiolosical environment of colon.

The results of *in vitro* drug release studies indicated that the drug release from the formulation H100 coated with hydroxypropylmethylcellulose alone takes place at a highly retarded rate. The cumulative amount of drug released from formulation H100 shows 6.71**%** drug release during the initial 5h of dissolution studies in simulated gastric (2h) and intestinal fluid (3h), and at the end of 24 h of the dissolution studies the tablets remains intact and mean percent drug released was 71**%**. The study shows that the formulation H100 fails to prevent drug releases in upper part of gastrointestinal tract and total amount of drug release in the target area colon is only 64% at the end of 24h, the drug release was incomplete and found to be time dependent from formulation H100. The decrease in drug release in the target area from formulation H100 compression coated with high proportion of hydroxypropylmethylcellulose might be due to swelling of the polymer forming a thick viscous stiff gel layer around the core tablet on being exposed to the dissolution fluids. This viscous gel layer will retards seeping of dissolution fluids into the core tablets and reduce the diffusion of drug from the core to negligible level and decreases the drug release from the formulation.

On the other hand, at the end of the 5h of dissolution study the percent of drug released from the formulation ED100 compression coated with ED alone were 11.21% and releases 97% of the drug after 24 h of dissolution study as shown in Figure 1. The release of 11.21% of drug in physiological environment of upper part of gastrointestinal tract from formulation ED100 is a serious consideration for drugs (for e.g., anticancer drugs) showing deleterious effects on stomach and small intestine. The formulation ED100 fails to retard drug release in physiological environment of stomach and small intestine and will not sustained the drug release in physiological environment of colon and releases majority of the drug within 18 h of dissolution study. This might be due to high pH dependent solubility (pH above 7) of ED present in the coat in the dissolution fluid phosphate buffer pH 7.4.

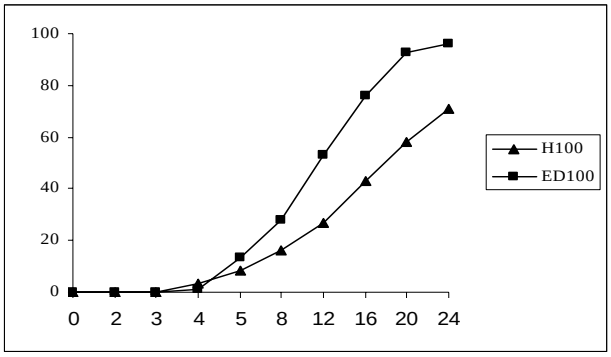

Figure 1. *In vitro* release profile of diclofenac sodium from tablets compression-coated with hydroxypropylmethylcellulose and eidragit® S 100

The drug delivery system targeted to colon should not only protect the drug being released in the stomach and small intestine, but they also should release and sustain the drug release in the colon. Hence an attempt has been made to prepare formulations HE91, HE82, HE73,HED64 and HED55 compression coated with HPMC–ED mixture in the ratio 9:1, 8:2, 7:3, 6:4 and 5:5 with an objective to retard the initial premature drug release in stomach and, small intestine and should give majority of the drug release in the colon (Figure 2).

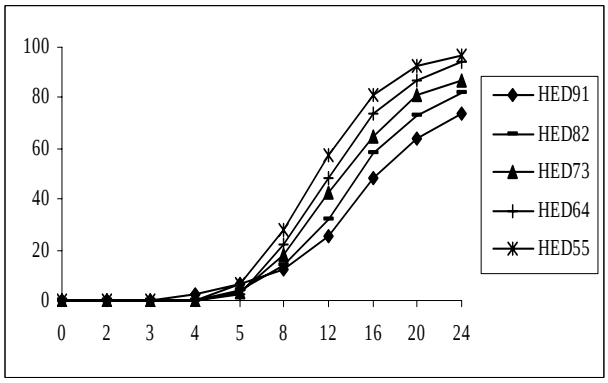

Figure 2. *In vitro* release profile of diclofenac sodium from tablets compression-coated with mixture of HPMC-ED mixture in different ratios

The cumulative amount of diclofenac sodium released from formulation HE91, HE82 and HE73 was 6.3% and 4.12% and 3.40% respectively after 5h of dissolution study. This indicates that HPMC-ED mixture as a compression coat is capable of minimizing the drug release in the physiological environment of stomach and small intestine. In spite of the high water solubility of diclofenac sodium, there was tight control of drug release in the physiological environment of stomach and small intestine. To assess the integrity / ability of coat the drug release studies were continued in phosphate buffer pH 7.4 for another 19 h. The mean percent of drug released at the end of 24 h of dissolution study from the formulation HE91, HE82 and HE73 was 74.5, 82.4%, 87.21% respectively.

The study clearly shows that as the proportion of HPMC decreases or ED increases in the coat formulation the percentage of drug release retarded in the upper part of gastrointestinal tract and the percentage of drug release in the physiological environment of colon was increased. This might be due to fact that on coming in contact with dissolution fluid, in first 5h of dissolution study eudragit® S 100 prevents initial swelling of HPMC present in the coat. After 5h of dissolution study ED dissolves, HPMC hydrates, swells up and, erodes and drug release increases in the colon target area. Hence the percentage of HPMC was decreased and percentage of eudragit® S 100 was increased with an increments of 10% in the coat formulation..

The cumulative amount of diclofenac sodium released from formulation HE64 and HE55 was 1.24% and 6.87% respectively after 5h of dissolution study. The mean percent of drug released at the end of 24 h of dissolution study from the formulation HE64 and HE55 was 94.34 and 97% respectively. The study shows that on further increasing proportion of eudragit® S 100 or decreasing the proportion of HPMC in the coat formulation HED55, the release of the drug at the end of 24 h dissolution study was increased but fails to control the drug release in upper part of gastrointestinal tract. The presence of insufficient amount of HPMC might have allowed solubilization of eudragid S 100 in the coat during initial 3h of the dissolution study in physiological environment of small intestine. This clearly shows that the drug release is due to solubility of ED, swelling and erosion of HPMC. Thus it is evident that unless the ED present in coat dissolved by pH of the dissolution media, drug release may not increase.

CONCLUSION

The core tablets compression-coated with HPMC and ED in the ratio 6:4 as a coat material released only 1.24 % of drug in the physiological environment of stomach and small intestine but released 92% of the drug in the target area i.e. physiological environment of colon . The presence of edragit® S100 in the coat reduces the initial swelling of HPMC which retards the drug release in physiological environment of upper part of gastrointestinal tract and, ensures complete release of drug in the colon due to its pH dependent solubility in dissolution fluids and the presence of HPMC sustained the drug release in the physiological environment of colon. Thus the tablets containing optimum proportion of HPMC and ED (6:4) is most likely to target diclofenac sodium to the colon with out being released significantly in stomach and small intestine.

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