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Research Article

EFFECT OF SUPERDISINTEGRATING AGENT AND OSMOGENS ON CIPROFLOXACIN LOADED NATURALLY OCCURRING BIODEGRADABLE COATED TABLETS FOR COLON TARGETING

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ABSTRACT

The aim of present study is to develop a controlled release site specific dosage form as tablet for treatment of colonic disease. There were two different phenomena used during the formulation of tablets. The first one was using of different super disintegrating agents (sodium starch glycollate, sodium cellulose methyl cellulose and sodium lauryl sulphate) as excipient in the core tablet. The amount of super disintegrant in the tablet and the coat weight were varied for the formulation of a suitable time-controlled release system. The second was development of different osmogen-based core tablets for drug delivery at the specific region of the colon. These core tablets were again coated with natural biocompatible polysaccharide polymers as a coating agent. Ciprofloxacin was used as a model drug for present study. In vitro drug release studies showed that super disintegrating agent (sodium lauryl sulphate 3.0 mg) containing formulation was more effective than other, because it showed burst effect and therefore a rapid drug release start as compared with sodium starch glycollate 3.0 mg containing formulation. The final result indicated all core tablets release drug fast, when it came at the colonic region within 12h and system follows as sustained drug delivery. Osmotic tablets were formulated with high concentration of osmogens; sodium chloride (OM-SC) and potassium chloride (OM-KC) and then coated with polysaccharide materials. These also were found to be useful for providing a sustained delivery of nearly 97% of the drug within 12h, but the release is too much fast than formulation prepared with all superdisintegranting agents. The coat weight required for protection in the upper gastrointestinal conditions varied from 10-20% of total weight of each tablets.

Keywords: Ciprofloxacin, Super disintegrating agents; Sodium lauryl sulphate, Sodium starch glycollate, Sodium carboxy methyl cellulose, Osmogen; Potassium Chloride, Sodium Chloride.

INTRODUCTION

Colon-specific drug delivery is mostly used for the treatment of colonic diseases, such as inflammatory or infectious bowel diseases or colon cancer[1]. From the last few decades, many researchers have interest in the field of colon-specific drug delivery for treatment of colonic disease. The interest of research is because the colon has a large amount of lymphoma tissue (which would facilitate a direct absorption into the blood), negligible brush border membrane peptidase activity, and much less pancreatic enzymatic activity as compared with the small intestine[2-4]. The colon also is considered as a suitable site for delivery of proteins, peptides, and acid labile drugs[5].

Targeting of drugs specifically to colon is advantageous in the treatment of diseases associated with the colon such as amoebiasis, Crohn's diseases, ulcerative colitis, and colorectal cancer. Site-specific drug delivery systems are the main focuses of oral controlled-release solid dosage forms[6]. The formulation based on approach slow delivery at the beginning of the dissolution process and fast release rate of drug in definite parts of the gastrointestinal tract and intestine increase local therapeutic effect[7]. Pulsatile drug delivery systems are characterized by two release phases. A first phase is nil or little amount of drug being released and a second phase is completely release of drug within a short period of time after a lag time. The release can be either time, or site-controlled[8].

Among many approaches for oral drug delivery to the colon site, pectin or their combination with natural biodegradable polymers based coated formulations show best effect, because they remain intact in the upper gastrointestinal tract and are degraded in the colon by colonic micoflora[1].

Enteric-coated systems provide the protection for drug release in the stomach. A thicker coat of these polymers on the delivery systems increase a lag phase of the formulation[9] Alternatively some drug release retarding agents can be introduced into the formulation by Sinha[10]. Osmotic agents generally have been used in the formulation to show burst effect.

The present study was developed by using superdisintegrants in the formulation as bursting agents, and these were evaluated against the osmogens based systems to show bursting effect. In vitro drug release studies were performed and drug release behavior characterized. The aim of the present system was to provide a rapid drug release with sustained effect after a lag time of 5–6 hr into the proximal part of colon. Because the proximal part of colon is the most absorptive site of the colon since the chyme is in a semi liquid form when formulation reaches at this part. Thus, the chance of drug absorption from this site is maximum[11]. The thicker coat of naturally biodegradable polymers providing a lag or silent phase of 5–6 h would be able to carry the dosage form into the proximal colon. The dosage form was designed with superdisintegrants and or osmotic agents (osmogens) for investigation rapid bursting effect of coated formulation, when system reaches into the proximal part of colon. The dissolution of the polymeric coating starts and a pressure starts to build up inside the tablet. When the pressure exceeds, the tablet bursts during the system transit through stomach and small intestine. The duration of this lag phase can be increased or decreased depending upon the site, where drug release is desired for local effect of drug for treatment of colonic disease. The bursting time of the tablet depend on coat weight thickness, combination of coating polymers, the quantity of superdisintegrant and the type of osmogen used. The quantity of the superdisintegrant in the tablet and the coat weight was varied and were evaluated for their drug release characteristics.

MATERIALS AND METHODS

Materials

Ciprofloxacin and Microcrystalline cellulose (Avicel PH 102) were obtained as gift sample from Plethico pharmaceutical pvt. Ltd, (Indore, India). Sodium starch glycollate and sodium carboxy methyl cellulose were obtained from plethico pharmaceutical pvt. Ltd., Indore, India. Other ingredients such as lubricant, glidant, and plasticizer used to prepare the tablet were of standard Pharmacopoeial grade and all chemical reagents used were of analytical grade.

Method

Solubility determination of ciprofloxacin

The solubility properties of ciprofloxacin were determined in water and at various pHs. Sodium thiosulphate was added to the medium, when pH 6.8 and pH 7.4 phosphate buffers were used to prevent oxidation. In earlier studies, sodium bisulphite, ascorbic acid and thioglycolic acid were also used, but they were abandoned, because of pH alterations. However, when sodium thiosulphate was used as an antioxidant, it did not affect the pH of the medium. Therefore, the

addition of sodium thiosulphate was kept constant for further studies, when the pH 6.8 or 7.4 buffers were used. The excess amount of ciprofloxacin was added to 100ml of medium and stirred continuously overnight at 37±0.5ºC.

The solubility values of ciprofloxacin in various media were determined spectrophotometrically. The UV detections were carried out at 200–400 nm, based on the previously obtained calibration curves. The solubility proflile of ciprofloxacin at various pHs medium shows in table 1[12].

Preparation of core tablets

Core tablets containing 250 mg of ciprofloxacin and superdisintegrant (SD) / osmogen (OM) were prepared with microcrystalline cellulose (Avicel 102) as filler by a wet compression method using starch paste as a binder. The wet granulation mass was passed through a mesh # 10 and dried at 60ºC for 1h in a hot air oven. The dried granules were sized by passing through a sieve # 14. These granules were collected and mixed with 5% magnesium stearate and 5% talc. These lubricated granules were compressed into tablets on single-station tablet punch machine (Modern Engineering New Delhi, India) using 4 mm deep concave and 1.2 mm round, flat and plain punches (Table 2)

Coating of tablets

The coating solution containing Guar gum, Xanthan gum and Pectin in the ratio of 1:1:2 was prepared in a mixture of 1:1 ethanol: water mixture using TEC (5% w/v) as plasticizer (Table 3). Gums containing mucilage stirred gently for a period of 10 min with magnetic stirrer. Dispersion was transferred to a filtering flask for air bubble removal by using a vacuum pump after complete homogenization. The core tablets containing ciprofloxacin were coated at different levels of coating by using spray pan-coat (Figure 1). Table 4 showed all details of the coating process parameters used for coating on formulation SD-C-A3. Samples were removed every hour and mean coating weight gain calculated. The coating process was repeated until the desired level coating weight was achieved.

After get best result from experimental result given in table 5, coating of such parameter used for all another formulations.

Disintegration test

Disintegration testing of tablets was carried out according to the Indian pharmacopoeia (1885) to identify the effect of disintegration agent in comparison to the osmotic agents (such as sodium chloride and potassium chloride) in carrying out the disintegration. Disintegration testing was carried out in phosphate buffer pH 6.8.

Bursting time

Bursting time was determined as the time noted visually, when the tablet coat was no longer able to withstand the internal pressure and the tablet opened up. The test was carried out in the dissolution media by keeping the tablets in buffer (pH 6.8) at 100 rpm at 37 ± 0.5 C. The test was carried out 6 tablets for each formulation.

In-vitro dissolution study

In-vitro dissolution study was performed on the tablets to identify the effects of different coating levels on release profiles of the tablets. The spray coated dosage form of ciprofloxacin was evaluated for their integrity in the physiological environment of stomach and small intestine under conditions mimicking mouth to colon transit. These studies were carried out using a IP dissolution rate test apparatus (apparatus type II, 50 rpm, 37±0.5ºC). The tablets were tested for drug release for 2 h in 0.1 N Hcl (900 ml) as the average gastric emptying time is about 2 h. Then the dissolution medium was replaced with pH 7.4 Sorenson's phosphate buffer (900 ml) and tested for drug release for 3 h as the average small intestinal transit time is about 3h. At the end of the time periods, two samples each of 1 ml were taken, suitably diluted and analysed for ciprofloxacin content at 269 nm using a double beam UV spectrophotometer (Shimadzu, UV-1800).

The susceptibility of gum combination coats to the enzymatic action of colonic bacteria was assessed by containing drug release studies in 100 ml pH 6.8 phosphate buffered saline to maintain colonic pH condition. At the end of the time periods, two samples each of 1 ml were taken, suitably diluted and analyzed for ciprofloxacin content at 271 nm using a double beam UV spectrophotometer (Shimadzu, UV-1800).

Characterization of release profile

Release profile of natural biodegradable coated polymers containing superdisintegrating agent and osmogens tablets were characterized for release lag time (T_{lag}) and release rate k. Release data within the linear range were selected and fitted to a zero-order mathematical model:

$$Q = C + kt$$

Where Q is the release percentage at time t; k is the slope of the fitted linear equation and here represents release rate; and C is the intercept of the linear equation. T_{lag} is defined as the time of the start of ciprofloxacin release and calculated here from the fitted equation, setting Q=0:

$$T_{lag} = - C / k.$$

The linear equation is based on regression of at least three release data, and only correlation coefficient of over 0.99 is acceptable for T_{lag} and k calculation[13].

RESULTS AND DISCUSSION

Disintegration test uncoated tablets

At the highest level, 3 mg of SD containing with SSG, the disintegration time was 3.54 min in buffer pH 6.8. The result of other formulations (tablets with sod. CMC, SLS), disintegration time was 4.56 min and 4.58 min, respectively (Table 6). The result depicts that the SD tablets disintegrate at faster rate than osmogen tablets, once the tablet coat dissolves during in-vitro release. Disintegration test carried out on coated tablets with lower coating level of 10% showed that disintegration time for tablets was greater than 185 min. This result pass disintegration test as prescribed under Indian pharmacopoeial standard for enteric coated tablet. Bursting times for each formulation with different levels of coating are given in Table 7.

***In- vitro* dissolution test on SD tablets**

All the formulation met the USP criteria for enteric performance test in 0.1N HCl (for 2 hr). In tablets containing 3 mg of superdisintegrant (SD-C) coated with 20% coating, SD-C-A3 tablets, and cumulative percent drug release was 1.95% in the first 5 h of the study, and this increased to 16.78% in 6 h and was 82.22% in 12 h. We observed that only 66.13% drug release from the formulation takes place in the 6–12 h intervals. The coating was decreased to 10% in SD-C-A1.5 tablets. SD-C-A1.5 tablets showed a cumulative percent drug release of 1.94% in the first 5 h of the study, which increased to 11.6% in 6 hr and was 93.44% in 12 h. We observed that only 81.87% drug release from the formulation takes place in the 6–12 h intervals. The above two results of SD-C-A3 and SD-C-A1.5 indicate that a 3-mg content of SD in the tablet shows the desired bursting time. In SD-C-A3 tablets, nearly 16% of drug release is observed between 2–6 h intervals showing rapid drug release. Similarly in SD-C-A1.5 tablets this rapid drug release period was between 2–7 h, showing nearly 17% drug release in these 7 h intervals. So, the coat weight was further increased for retardation of release containing 1.5% super disintegrating agent as SSG. The dissolution profiles of ciprofloxacin tablets containing 3 mg of SD (SD-C-A3, SD-C-B3, and SD-C-C3) are shown in Figure 2. Results show that by increasing the coat weight to 20% in SD-C-A3, B3 and C3 tablets the rapid release period depend on nature and concentration of various super disintegrating agent given in table 2, and the rapid release was seen in 5–11 h interval with more than 70% drug release in this period. To reduce the coat weight, the amount of SD in the tablet was reduced to 1.5 mg. The tablets SD-C-A1.5 containing 1.5 mg of SD, coated to 10% coat weight, showed a cumulative percent drug release of 1.95% in the first 5 h of the study, which increased to 11.64% in 6 hr and was 93.44% in 12 h. We observed that 92% drug releases from the formulation takes place in the 6–12 h intervals, because depend on formulation coated with 10% coat weight passage through colonic environment. The lag time for drug release from the formulation was = 6 h (Figure 3).

Table 1: The solubility values of ciprofloxacin at various pH medium

Media	Solubility (mg/ml)	Mean	Relative standard deviation %	Standard error of Mean (SEM)	Lower 95% confidence interval	P Value
Water	2.323	2.348	0.0279	0.0114	2.319	> 0.01
0.1 N Hcl	2.786	2.7866	0.0237	0.0096	2.762	> 0.01
pH 4.5	0.0121	0.126	0.00045	0.000183	0.0121	> 0.01
pH 6.8	0.0110	0.0116	0.000388	0.000158	0.011	> 0.01
pH 7.4	0.1698	0.1678	0.0042	0.00171	0.1630	> 0.01

Table 2: Formulation code and the percentage superdisintegrating agent / osmotic agent present in the core tablet

Formulation code	% Superdisintegrating agent in the tablet			% of osmotic agent in the tablet	
	Sodium starch glycollate	Sodium carboxy methyl cellulose	Sodium lauryl sulphate	Sodium chloride	Potassium chloride
SD-C-A1.5	1.5	-	-	-	-
SD-C-B1.5	-	1.5	-	-	-
SD-C-C1.5	-	-	1.5	-	-
SD-C-A3	3	-	-	-	-
SD-C-B3	-	3	-	-	-
SD-C-C3	-	-	3	-	-
OM-C-SC 1	-	-	-	92	-
OM-C-KC 1	-	-	-	-	92
OM-C-SC 2	-	-	-	92	-
OM-C-KC 2	-	-	-	-	92

SD = superdisintegrant, OM = osmotic agent, KC = potassium chloride, SC = sodium chloride.

Table 3: Coating variables and combination of polymers and the percent coat weight

Formulation code	Combination of polymers	% coat weight
SD-C-A1.5	Guar gum, Xanthan gum and Pectin in the ratio of 1:1:2	10
SD-C-B1.5		10
SD-C-C1.5		10
SD-C-A3		20
SD-C-B3		20
SD-C-C3		20
OM-C-SC 1		10
OM-C-KC 1		10
OM-C-SC 2		20
OM-C-KC 2		20

The small amount of disintegrant is unable to exert its effect within the desired time. Considering the normally accepted GI transit time, 2 h for stomach and 3–4 h for small intestine, the SD-C-A1.5 and SD-C-A3 formulations release the drug directly into colon. The increase in retard time of SD-C-A3 tablets containing 3 mg of SD was due to increase in coat weight. The disintegration and dissolution time depends on the coating thickness[14], as well as the amount of SD added. The coat weight of these systems may seem to be very less with compression coated systems; the coat weight may more than 200% of the core. The present study shows that the dissolution time can be retarded by increasing the coating thickness[14] as well as the amount and nature of SD added. The release of drug from the coated tablets can be attributed to pore formation and bursting of the coat due to the presence of SD. The bursting of tablets with SD occurs because of rapid uptake of water from the pores, followed by swelling due to capillary action[15]. Cross-linked PVP, when added to the formulation has enhances dissolution of poorly soluble drugs from solid dosage forms[16]. This might have contributed to the faster dissolution. The r^2 value and T_{lag} time of all formulation containing super disintegrating agents were showed in table 8.

In- vitro dissolution test on osmogen tablets

The formulation which containing potassium chloride osmogen with a coat weight of 10%, OM-C-KC 1 tablets, the cumulative percent drug release was found to be 7.88% in the first 4.45 h of the study and release was too much faster with a total of 96.25% of drug was released in 12h. These systems seem quite promising for a sustained delivery of drug into the colonic region (Figure 4). To refine these systems further, the coat level was increased. When coating was increased from 10 to 20% (OM-C-KC 2), a cumulative percent drug release of 6.88% was found in the first 4.32 h of the study and showed burst effect, the release of drug increased up to 94.22% in 12h (Figure 5). These results may be attributed to the fact that an increase in coat weight led to decreased seeping of water into the tablet, due to a delayed pore formation in thicker coats. Thus, the tablets are not able to release the complete drug within the usual colonic transit time about 18h.

Tablets containing sodium chloride (OM-C-SC 1) coated to 10% showed a cumulative percent drug release of 14.44% in the first 4.38 h of the study, which increased to 99.32% in 12h. We observed that 83% drug was released from the formulation in the 6–12h intervals. When coating was increased further from 10 to 20% in OM-C-SC 2 tablets, a cumulative percent drug release was 12.44% in the first 4.40 h of the study and was 96% in 12h. We observed that 82% drug release from the formulation takes place in the 6–12h interval. The dissolution profiles of ciprofloxacin tablets containing sodium chloride (OM-C-SC 1 and OM-C-SC 2) are shown in Figure 4 and 5. This may be explained similarly as in OM-KC tablets. Even though sodium chloride has a higher osmotic pressure than potassium chloride, it requires lower percentage of coating for complete release of drug. At 16% of coating, the release of drug was found to be 99.37% in 12h. But after increasing the coat weight to 24%, the release was retard to 96.88% in 12h. The release from sodium chloride tablets was significantly similar but faster as compared with potassium chloride tablets at approximately the same coating level. The release of drug from the tablets containing osmogens is due to development of hydraulic pressure; when dissolution medium imbibe the osmogen, it exerts hydraulic pressure on the film and ruptures the coating. The r^2 value and T_{lag} time of all formulation containing super disintegrating agents were also showed in table 8.

Fig. 1: Fabricated coating pan for coating of ciprofloxacin tablets

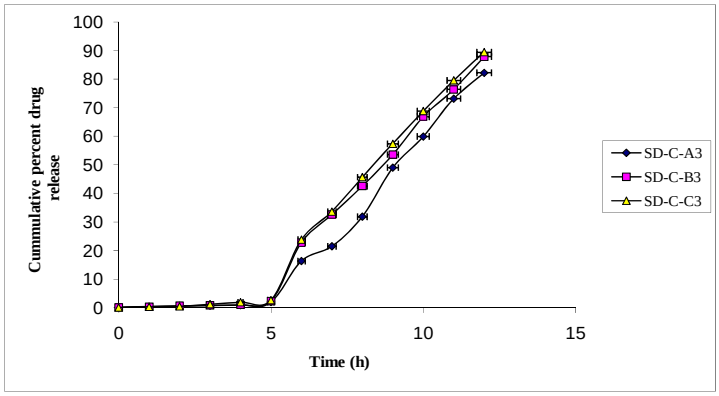

Fig. 2: Cummulative percent drug release versus time profile of SD-C-A3, SD-C-B3 and SD-C-C3

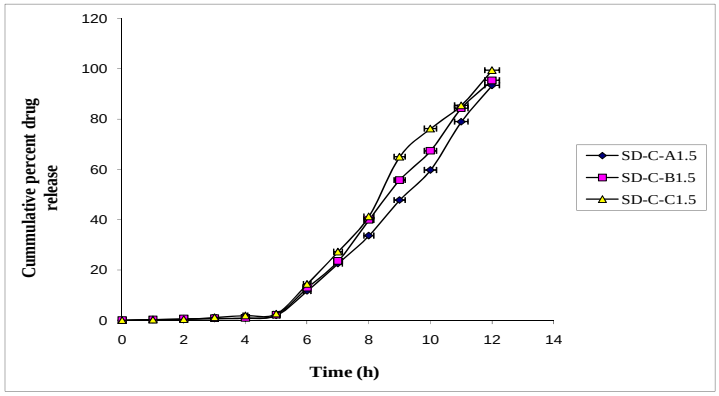

Fig. 3: Cumulative percent drug release versus time profile of SD-C-A1.5, SD-C-B1.5 and SD-C-C1.5.

Table 4: Selection of levels of independent variables of coating parameters for coating of polysaccharide polymer on SD-C-A3 formulation (weight gain 20%)

Independent variables	Level	
	A	B
Atomizing pressure (bar)	1	1
X1, Inlet temperature (ºC)	40	50
Bed temperature (ºC)	25	35
X2, Pan speed (rpm)	50	75
Spray rate (g/ml)	10	10
Drying in the equipment after coating (min)	15	15
Final drying in oven	60ºC for 1 h	60ºC for 1 h

Table 5: Matrix of experimental design and result of study of SD-C-A3 formulation

Exp.	X1	X2	Tablet thickness		Coating time (h)	Hardness	Drug release t50% (h) mean ± SD & lower 95% confidence interval
			Height (cm)	Width (cm)			
1	A	B	0.60	1.32	1.46	6.2	9.16 ± 0.03533 & 9.077
2	B	A	0.62	1.41	1.25	6.5	9.22 ± 0.05568 & 9.032
3	A	A	0.59	1.36	1.37	5.9	9.11 ± 0.0916 & 8.902
4	B	B	0.62	1.34	1.31	6.4	9.01 ± 0.05033 & 8.932

Table 6: Disintegration time of tablet uncoated cores tested in phosphate buffer pH 6.8 (n=6)

Formulation	Time (min)
Tablets with 1.5 mg of SSG superdisintegrant	3.13
Tablets with 3.0 mg of SSG superdisintegrant	3.54
Tablets with 1.5 mg of sod. CMC superdisintegrant	4.18
Tablets with 3.0 mg of sod. CMC superdisintegrant	4.56
Tablets with 1.5 mg of SLS superdisintegrant	4.03
Tablets with 3.0 mg of SLS superdisintegrant	4.58
Tablets with sodium chloride	6.54
Tablets with potassium chloride	8.12

Table 7: Bursting time of various coated formulations (n = 6)

Formulation code	Time (h)
SD-C-A1.5	5.02
SD-C-B1.5	5.08
SD-C-C1.5	5.20
SD-C-A3	5.05
SD-C-B3	5.18
SD-C-C3	5.25
OM-C-SC1	4.38
OM-C-SC2	4.24
OM-C-KC1	4.45
OM-C-KC2	4.32

Table 8: Release characteristics of zero-order kinetics fitting at different factor levels

Factor	Factor level	Time span	r	T_{lag} (h)	k
SSG content in core tablet	1.5 mg	5.22-12	0.990	4.90	13.13
	3.0 mg	5.20-12	0.990	4.31	11.95
Sod. CMC content in core tablet	1.5 mg	5.12-12	0.996	5.03	13.78
	3.0 mg	5.05-12	0.991	4.38	11.69
SLS content in core tablet	1.5 mg	5.09-12	0.990	5.16	14.33
	3.0 mg	5.01-12	0.991	4.89	11.54
Coating weight of Sodium chloride core tablet	10	4.13-12	0.991	3.46	12.74
	20	3.45-12	0.991	4.08	12.58
Coating weight of Potasium chloride core tablet	10	4.05-12	0.990	4.33	12.19
	20	3.50-12	0.991	4.31	12.07

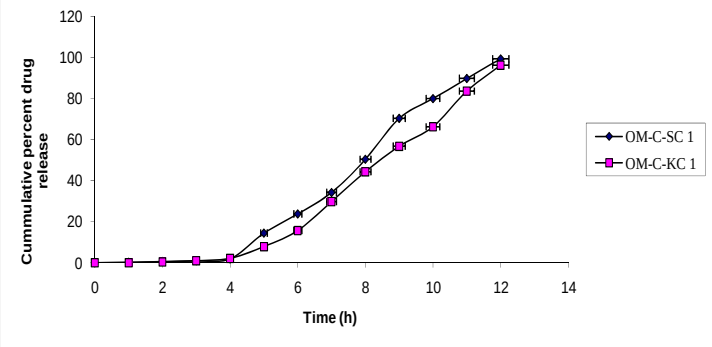

Fig. 4: Cumulative percent drug release versus time profile of OM-C-SC 1 and OM-C-KC 1.

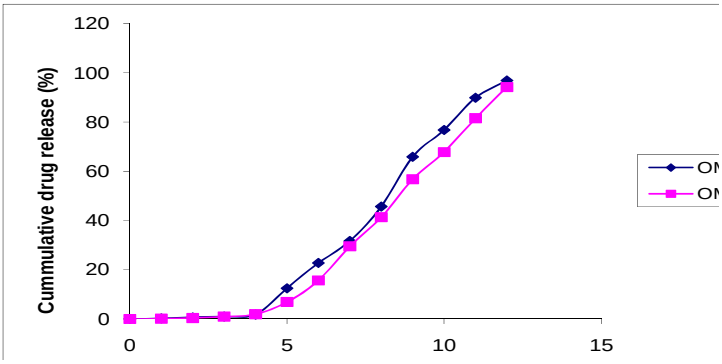

Fig. 5: Cumulative percent drug release versus time profile of OM-C-SC 2 and OM-C-KC 2.

CONCLUSION

The presence of superdisintegrant/osmotic agent inside core formed time-controlled drug delivery systems that could facilitate drug delivery into different segments of the GIT depending upon the coat weight and the concentration of these agents. Fast burst tablets could be formulated making use of SDs rather than osmogens. Presence of 3mg SD in the tablet coated to a coat weight of 20% formed fast release tablets facilitating drug release in the proximal colon. The coat weight determines the silent/lag phase of the formulation, whereas the coat weight and amount of SD in the tablet determines the burst effect and rapid/sustained drug release.

Osmotic tablets could be formulated making use of potassium chloride/sodium chloride in the core tablets and further coated with polysaccharide polymers. A coat weight of 10% in sodium chloride tablets would deliver 83% of the drug into the colonic region in a sustained manner. In potassium chloride tablets, a coat weight of 10% facilitated the delivery of more than 82% of drug into the colonic region. According all the results conclude that the formulation containing superdisintegrating agents showed a best drug delivery system for colon targeting.

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