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Research Article

FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY OF BUDESONIDE USING MODIFIED CODES SYSTEM

Krutika A. Kulkarni[1]., Jaymin Patel[2] and Shreeraj Shah[3]

[1]Yogivilla, Manjalpur Baroda, Gujarat, India
[2,3]LJ Institute of Pharmacy, Ahmedabad, Gujarat, India

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ABSTRACT

The purpose of this study was to prepare budesonide tablet to deliver the drug to colon in intact form which is used to treat IBD, ulcerative colitis, Chron's disease. In present study budesonide tablets were prepared using CODES Technology for targeting the drug to colon. The core tablets were prepared using natural polymer Karaya gum which gets degraded by colonic enzymes. Tablet is coated with Eudragit E100 and super coated with Eudragit S100 which will retard the drug release in upper GI Tract and in 6.8pH phosphate buffer in presence of rat caecal micro flora it gave the drug release. The formulation batches were prepared by BOX-BEHNKEN Factorial Design using 3 independent variables X1(con. of Karaya gum), X2 (%wt. gain by Eudragit E100), X3 (% wt. gain by Eudragit S100) and Dependent variable Y5 (% drug release in 5hr) and Y12 (% drug release in 12hr). On the basis of criteria that, not more than 5% drug should release within 5hr (Y5). Where F8 batch was decided as optimized batch because only 2% drug released within 5hr. The result showed that optimized formulation had delivered the maximum amount of drug to the colon in intact form.

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INTRODUCTION

Site-specific delivery of drugs to the site of action has the potential to reduce side effects and to increase pharmacological response. One of the seemingly interesting areas to target drugs through oral route is the colon. Various systems have been developed for colon-specific drug delivery: covalent linkage of a drug with a carrier, coating with pH-sensitive polymers, time-dependent release systems, and enzymatically controlled delivery systems. Enteric-coated systems are the most commonly used for colonic drug delivery, but the pH difference between the small intestine and colon is not being very pronounced leading to poor site specificity. The drawback of the time-dependent release system is its inability to sense any variation in the upper gastrointestinal tract transit time; besides, any variation in gastric emptying time may lead to drug release in the small intestine before arrival to the colon. There is a steep gradient of enzyme activity along the gastrointestinal tract; these enzymes are derived from gut microflora. In humans, the stomach and small intestine contain roughly 103–104 colony forming units (CFU)/mL. However, the concentration of microflora rises dramatically passing from the terminal ileum to the ascending colon where the numbers reach 1,011–1,012 CFU/mL. These bacteria survive and thrive by fermenting a wide range of substrates (e.g., oligosaccharides, polysaccharides, mono polysaccharides) left undigested in the small intestine. Hence, enzymatically controlled delivery systems is considered a convenient approach for site-specific drug delivery to the colon where no drug release can occur unless the system arrives to the colon (7–9). BUD is a potent corticosteroid that has important implications in the pharmacotherapy of inflammatory bowel disease, especially in the treatment of ulcerative colitis and Crohn's disease. BUD is approximately twice as active as beclomethasone dipropionate, and it is over 1,000 times more active than either prednisolone or hydrocortisone in inducing intracutaneous vasoconstriction (as a marker of anti-inflammatory activity). BUD is commercially available in the market in the form of enteric-coated preparations mainly for the treatment of small intestine active Crohn's disease. However, these products, similar to other available site-specific dosage forms, are not sufficiently selective to treat colonic inflammatory bowel disease. It was found that less than 5% of the drug was available beyond the ileum and cecum, and therefore, colonic delivery still needs to be optimized by a more reliable colon-specific system. Previous workers have developed BUD microparticles for colon delivery. However, being relatively complex systems, their large-scale manufacturing requires a lot of technological

Corresponding author:* **Krutika A. Kulkarni
Yogivilla, Manjalpur Baroda, Gujarat, India

advancement and skills. So, an attempt was made to formulate spray coated tablets, which could be formulated easily, using the usual tableting techniques The aim of the present study was to formulate BUD compression-coated tablets to prevent drug release in the stomach, had an additional lag phase to retard drug release in the small intestine, and to deliver drug specifically to the colon. Enzymatically controlled delivery systems were developed using karaya gum and Eudragit E100 and Eudragit S100 by spray coating. With the coating of EUD E100, EUD S100, with karaya gum natural polysaccharide as a core tablet polymer was tried in an attempt to optimize drug release in the colon.

MATERIALS AND METHODS

Materials

Budesonide obtained as gift sample from Sun Pharmaceutical IND. LTD-Panoli (batch no. USP PNBDNFL 17007), Karaya gum obtained as gift ample from Yarrow chem. Coating polymers Eudragit E100 and Eudragit S100 obtained from Evonik India Pvt Ltd.

Study of the Flow Properties of the Powder Blends Used in Tablets

The flow properties of the different powder blends used in the core tablets was studied using angle of repose (fixed height cone method), Carr's compressibility index, and the Hausner ratio methods.

Preparation of Budesonide core tablet

Core tablets containing 9 mg of budesonide were prepared with karaya gum as polymer and lactose monohydrate as the main filler/constituent using direct compression method. The tablets were evaluated for appearance, uniformity of weight, hardness, friability to meet predetermined criteria suitable for coating. Batches were prepared applying Box-behnken Factorial design.

Preparation of Factorial Design

Preparation of Formulation by Using Box-Behnken Factorial Design

Factorial Design

It is well known that traditional experimentation involves great effort and time especially when complex formulations need to be developed. It is desirable to develop an expectable pharmaceutical formulation in shorter period of time using minimum no of man power and raw materials. In the present study batches prepared by 3^3 factorial design was employed to study the effect of independent variable i.e. concentration of Karaya Gum (X1), %Wt. gain by Eudragit E100 (X2), %Wt. gain by Eudragit S100 on dependent variables of % drug release at 5hrs. (Y_5) and % drug release at 12 hrs. (Y_{12}).

Levels and variables of Box Benchen Factoril Design

Table 1 Levels and variables

Concentration of Independent variable			
Level	**Factor 1(Conc. Of Karaya Gum)**	**Factor 2(% Wt. gain of Eudragit E100)**	**Factor 3(% Wt. gain of Eudragit S100)**
-1	60	1.5	0
0	70	3	5
1	80	4.5	10
Dependent Variable			
Y_5	% Drug release at 5hrs.		
Y_{12}	% Drug release at 12hrs.		

Table 2 Factorial batch

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Budesonide(mg)	9	9	9	9	9	9	9	9	9	9	9	9	9	9	9
Karaya(mg)	60	80	60	80	60	80	60	80	70	70	70	70	70	70	70
Lactose(mg)	78	58	78	58	78	58	78	58	68	68	68	68	68	68	68
Magnesium Stearate(mg)	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
Aerosil(mg)	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Total(mg)	150	150	150	150	150	150	150	150	150	150	150	150	150	150	150
Eudragit E100 %wt. gain	1.5	1.5	4.5	4.5	3	3	3	3	1.5	4.5	1.5	4.5	3	3	3
Eudragit S100 %wt. gain	5	5	5	5	0	0	10	10	0	0	10	10	5	5	5

Coating of the Tablets

Spraying dispersions for coating were prepared as described in the previous report for coating with Eudragit E100 as enteric coating and Eudragit S 100 as subsequent coating. Coating was done in different % concentration as per factorial design batches. Eudragit E100 was in range of in different range of 1.5, 3, and 4.5 %wt. again where Eudragit S100 as 0, 5, 10 %wt. gain

Coating solution

Enteric coating solution of Eudragit E 100

Table 3 Enteric coating solution of Eudragit E 100

Ingredients	Amount
Eudragit E 100	5gm
Talc	1%
PEG	5%w/w
Color	q.s.
Acetone	50ml
IPA	50ml

Eudragit S 100 coating solution

Table 4 Enteric coating solution of Eudragit S 100

Ingredients	Amount
Eudragit S 100	5gm
Talc	1%
PEG	5%w/w
Color	q.s.
Acetone	50ml
IPA	50ml

Method used for coating study

In present study Spray coating method was used for coating of the tablets.

1. Required quantities (100 no.) of tablets were loaded in coating pan.
2. Pan rpm was set to 35-40 rpm and temperature adjusted 50ºC
3. For the proper coating spray gun was adjusted over tablets, than started the spraying pf solution. After spraying coated tablets were collected from the pan.

Various parameters under the coating were as follows.

Table 5 coating parameters

Parameter	Value
Inlet Air temperature	50-55ºC
Exhaust temperature	30-35ºC
Atomization (bar)	2
Spray rate	10
Pan RPM	35-40

Post compression parameters of tablet

Dissolution Test

Experiments were performed to study the effect of (a) coating formulations, (b) pH of the dissolution media, and (c) GI pH variability among individuals on drug release profiles of the tablets. The experiments were carried out in dissolution test apparatus (Type 2 Paddle type) at 50 rpm, 37°C) for 2hrs in

0.1N HCL (900 ml) as the average gastric emptying time is 2hrs. Then the dissolution medium was replaced with 7.4 ph phosphate buffer solution (900ml) and tested for 3hrs as the average intestinal transits time is 3hrs. And finally the dissolution medium was replaced with 6.8ph Phosphate buffer solution (900ml) containing rat caecal content. At the end of each time interval, 5ml of samples were withdrawn and 5ml fresh media was added and samples were analyzed using UV spectrometer at 243nm.

Stability Study

Post compression parameters of an optimized batch were calculated on 0 day of the study and after 30 day of study. Result are mentioned in the table. Comparison was done between 0 day and 30 day results.

RESULT AND DISCUSSION

Standard Calibration of Budesonide

Standard plot of Budesonide using 0.1N HCL as solvent

Standard calibration curve of drug in 0.1N HCL was depicted as in figure. The data are as shown below. The data is correlated with coefficient (R^2) of 0.9969

Table 6 calibration of budesonide in 0.1 N HCL

Concentration (µg/ml)	Absorbance at 244nm ±SD (n = 3)
2	0.268±0.002
4	0.331±0.0016
6	0.404±0.008
8	0.455±0.002
10	0.514±0.0018

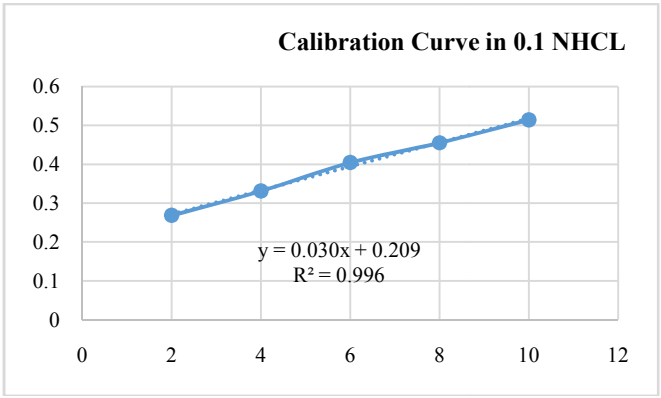

Fig 4 Standard calibration curve in 0.1 N HCL

Standard plot of Budesonide using 7.4 Phosphate Buffer

Standard calibration curve of drug in 7.4 pH phosphate buffer was depicted as in figure. The data are as shown below. The data is correlated with coefficient (R^2) of 0.9977

Table 7 calibration of budesonide in 7.4pH Phosphate buffer

Concentration (µg/ml)	Absorbance at 244nm ±SD (n = 3)
2	0.248±0.0016
4	0.362±0.0021
6	0.453±0.0021
8	0.566±0.0012
10	0.689±0.0015

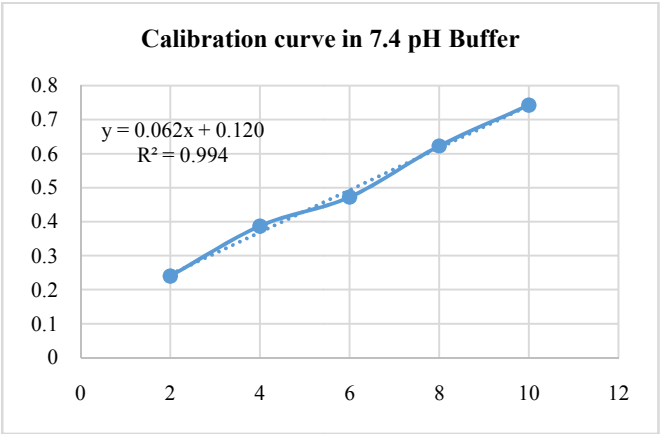

Fig 5 Standard calibration curve in 7.4 pH Phosphate buffer

Standard plot of Budesonide using 6.8 pH Phosphate Buffer:-Standard calibration curve of drug in 0.1N HCL was depicted as in figure. The data are as shown below the data is correlated with coefficient (R^2) of 0.9947

Table 8 calibration of budesonide in 7.4pH Phosphate buffer

Concentration (µg/ml)	Absorbance at 244nm ±SD (n = 3)
2	0.24±0.007
4	0.387±0.008
6	0.472±0.0011
8	0.622±0.002
10	0.71±0.0012

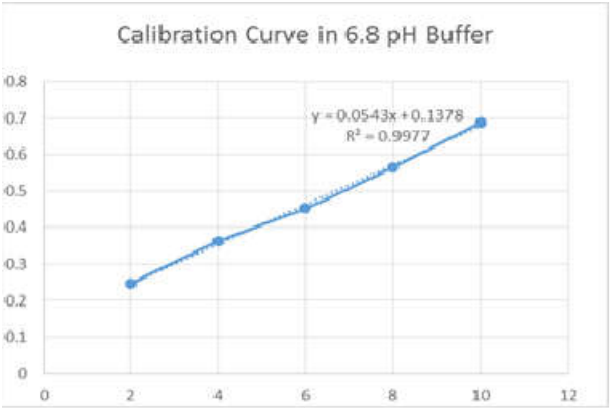

Fig 6 Standard calibration curve in 6.8 ph phosphate buffer

Physical Properties of Drug and Excipients

Table 9 Pre compression parameters

Parameters	Bulk Density $(g/cm)^3$	Tapped Density $(g/cm)^3$	Hausner's Ratio	Angle of Repose	Carr's Index (%)
F1	0.67	0.83	1.23	24.44	14.28
F2	0.71	0.89	1.25	26.56	15.20
F3	0.55	0.62	1.12	23.37	12.48
F4	0.64	0.75	1.17	24.22	14.12
F5	0.64	0.88	1.21	23.64	13.98
F6	0.66	0.74	1.23	25.19	14.29
F7	0.59	0.78	1.11	23.24	15.28
F8	0.68	0.84	1.16	24.16	12.42
F9	0.58	0.67	1.24	24.32	12.27
F10	0.67	0.63	1.26	25.42	13.42
F11	0.70	0.74	1.15	23.27	15.44
F12	0.68	0.68	1.15	24.12	14.28
F13	0.67	0.63	1.17	24.32	13.60
F14	0.58	0.61	1.11	22.41	14.69
F15	0.64	0.76	1.12	23.55	16.11

In-vitro Evaluation of Factorial batches F1 to F5

Table 10 Drug release of batch F1 to F5

Dissolution medium	Time(hr)	%Cumulative drug release				
		F1	F2	F3	F4	F5
0.1 N HCL	1		1.27	1.19		
	2	1.03	2.24	2.16	0.14	3.2
7.4ph Phosphate buffer	3	2.22	3.65	6.74	1.48	3.45
	4	3.71	15.95	9.21	2.62	4.91
	5	4.98	13.07	16.02	3.901	89.77
	6	26.11	30.27	27.29	22.5	94.11
6.8ph Phosphate buffer with 4%ceacal content	7	33.4	35.4	30.24	25	99.27
	8	59.62	47.23	40.28	39.12	
	9	67.83	53.27	54.67	40.22	
	10	78.6	69.12	65.35	21.04	
	11	80.72	84.26	76.45	68.45	
	12	87.22	89.94	86.44	82.3	

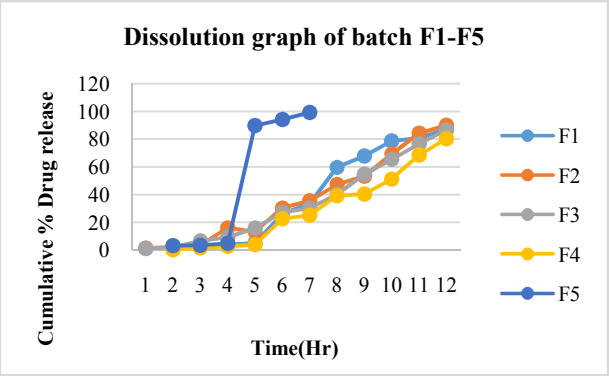

Fig 7 Drug release of batch F1 to F5

In-vitro Evaluation of Factorial batches F6 to F10

Dissolution medium	Time (hrs.)	%Cumulative drug release				
		F6	F7	F8	F9	F10
0.1 N HCL	1			1.19	4.7	
	2	1.03	0.24	2.16	16.14	3.2
7.4ph Phosphate buffer	3	2.22	0.65	6.74	18.48	3.45
	4	3.71	1.5	9.21	25.62	4.91
	5	4.98	2.11	16.02	89.94	79.77
	6	26.11	30.27	27.29	94.6	94.11
6.8ph Phosphate buffer with 4%ceacal content	7	33.4	43.4	37.24	98.22	98.99
	8	59.62	55.23	42.28		
	9	67.83	69.27	54.67		
	10	78.6	78.12	65.35		
	11	80.72	84.26	76.45		
	12	90.22	98.97	85.3		

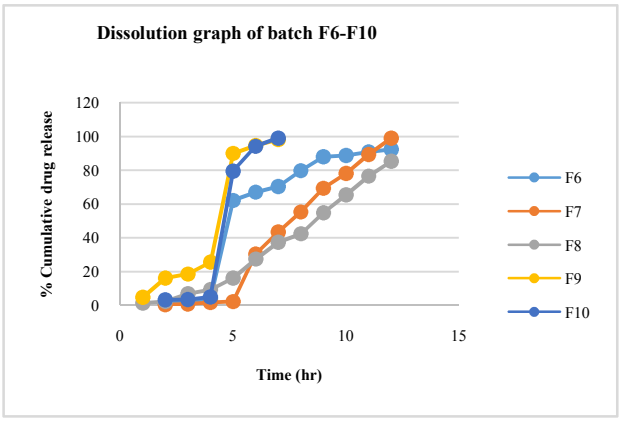

Fig 8 Drug release of batch F6 to F10

In-vitro Evaluation of Factorial batches F11 to F15

Table 11 Drug release of batch F11 to F5

Dissolution medium	Time(hr)	%Cumulative drug release				
		F11	F12	F13	F14	F15
0.1 N HCL	1		1.27	1.19		
	2	1.03	2.24	2.16	0.14	3.2
7.4ph Phosphate buffer	3	2.22	3.65	6.74	1.48	3.45
	4	3.71	15.95	9.21	2.62	4.91
	5	4.98	13.07	16.02	3.901	89.77
	6	26.11	30.27	27.29	22.5	94.11
6.8ph Phosphate buffer with 4%ceacal content	7	33.4	35.4	30.24	25	99.27
	8	59.62	47.23	40.28	39.12	
	9	67.83	53.27	54.67	40.22	
	10	78.6	69.12	65.35	21.04	
	11	80.72	84.26	76.45	68.45	
	12	87.22	89.94	86.44	82.3	

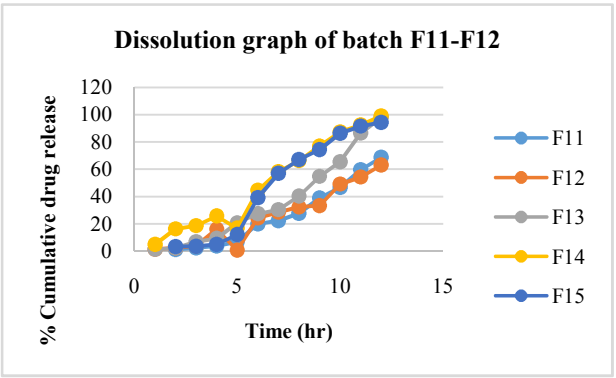

Fig 9 Drug release of batch F11 to F15

Optimization of batch on the basis of release profile of drug

The in-vitro drug release shows 100% drug release in pH 6.8 buffer with caecal content up to 12hrs. Drug release before completion of lag time was found to be less than 5%. The result obtained in the in-vitro drug release study tabulated in the table to and also the graphical response represented in fig to. The drug release profile showed sigmoid release pattern which is considered to be ideal for colon drug delivery system.

According to the cumulative drug release, F7 F8 and F12 were optimized because of we compare drug release of all the batches batch 5 10 and 10 show release 89.77%, 89.84% , 79.44% drug release within 5hrs which is not proper for the colon targeting. And rest all batches are also going out of acceptance limit of release of drug more than 5% within 5hrs.In batch F7 F8 and F12 there is less than or near to 2% drug release obtained but considering the Dependent variable Y12 the release of F12 batch is only 63% at 12hrs which cannot be accepted. So batch F7 and F8 are optimized one where further again considering the release of F7 (98.25%) batch was greater than F8 batch (85%). F8 batch was considered the Optimized one.

Surface Response curve of X1 X2 and X3 variables at Y5 and Y12 hrs

Surface response curve of dependent variable Y5

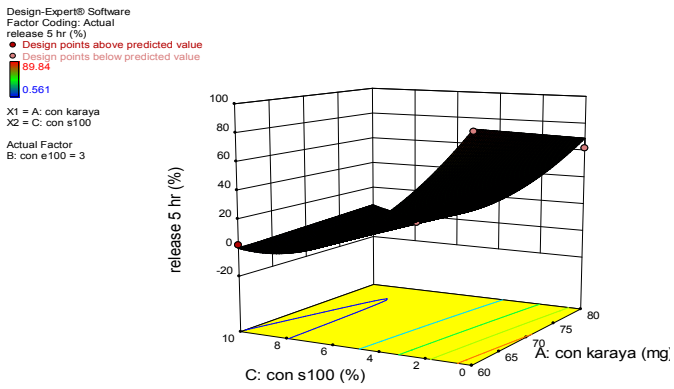

Fig 10 Response curve of effect of X1 X2 and X3 on Y5

Surface response curve of dependent variable Y12

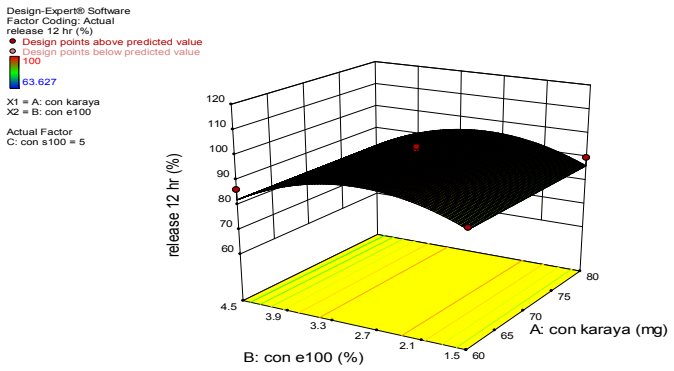

Fig 11 Response curve of effect of X1 X2 and X3 on Y12

Equation

Full Model

Y5=16.47-3.89x1-1.82x2-38.63x3-5.05x1x2+7.10x1x3+1.10x2x3-5.96x1^2-1.01x2^2+28.65x3^2

Y12 = 97.11-3.15x1-2.08x2-9.30x3-2.23x1x2-1.42x1x3-1.02x2x3+0.039x1^2-11.19x2^2-3.08x3^2

Stability Study for an Optimized batch

Post compression parameters of an optimized batch were calculated on 0 day of the study and after 30 day of study. Result are mentioned in the table. Comparison was done between 0 day and 30 day results.

Table 12 Post compression parameters of optimized batch

Parameter	At day 0	At day 30
Hardness	6	6
% Friability	0.39	0.40
%drug content	96.52	96.50

Comparison of invitro release profile at day 0 and day 30

Table 13 Comparison of invitro release profile

Time	%CDR at day 0	%CDR at day 30
1	0	0
2	0	0
3	0.65	0.69
4	1.5	1.7
5	2.11	2.14
6	30.27	31.2
7	35.4	36.24
8	47.23	48.1
9	53.27	53.4
10	69.12	70.21
11	84.23	84.25
12	98.97	97.12

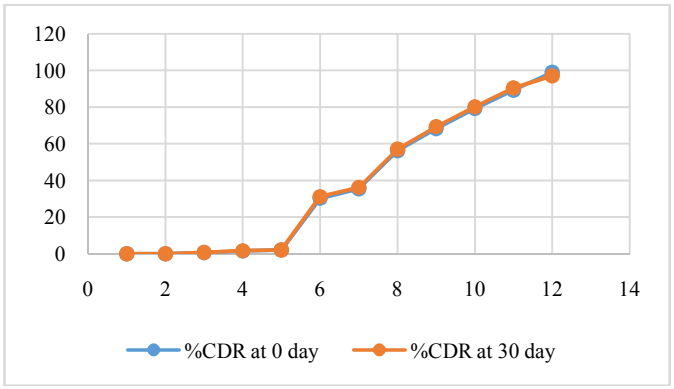

Fig 12 Comparison between dissolution profiles of optimized batch

Comparison between dissolution profile of optimized batch at day 0 and day 30

The percentage of drug elease before and after storage was found to be similar. Dissolution profiles before and after storage are nearly overlapping. The change in the drug release pattern i.e. was not that significant difference of the tables tested after 30 daysfrom the dissolution profile of optimized batch tested before a month.

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