International Journal of Current Advanced Research
ISSN: O: 2319-6475, ISSN: P: 2319-6505, Impact Factor: 6.614
Available Online at www.journalijcar.org
Volume 7; Issue 4(B); April 2018; Page No. 11381-11386
DOI: http://dx.doi.org/10.24327/ijcar.2018.11386.1968

Research Article

FORMULATION AND EVALUATION OF COLON TARGETED DRUG DELIVERY OF EXENATIDE

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A R T I C L E I N F O

Article History:

Received 15th January, 2018
Received in revised form 13th February, 2018 Accepted 8th March, 2018
Published online 28th April, 2018

Key words:

Colon targeted drug delivery, pH dependent approach, Exenatide, Eudragit S100, HPLC method

A B S T R A C T

The purpose of this study was to prepare tablet of Exenatide to deliver the drug to the colon in intact form which is used for the treatment of Type II diabetes. Type II diabetes is a chronic progressive disorder characterized by defective insulin secretion and increased insulin resistance. The drug Exenatide is very useful for the management of type II diabetes and also reduces the complications which are majorly observed in this disease i.e. conversion from Type II to Type I. As this drug is not as much stable in gastric pH because instead of absorption in blood it will get degraded in acidic environment so it is targeted to colon as colon shows best absorption for the macromolecular drugs.

In the present study, Exenatide tablet was formulated using approach of pH dependent drug delivery for targeting drug to the colon. The core tablets were prepared by using Protease inhibitor and Adsorption enhancer i.e. Na-EDTA and Chitosan which will get easily degraded by colonic enzymes. Tablet was compress coated by Eudragit S100 and Guar gum which will retard the drug release in upper GI Tract and in 6.8 pH it will give the drug release. The formulations of the batches were prepared.

INTRODUCTION

Targeted drug delivery into the colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs. The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route to the colon i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon. The colon is believed to be a suitable absorption site for peptides and protein drugs for the following reasons; (i) less diversity, and intensity of digestive enzymes, (ii) comparative proteolytic activity of colon mucosa is much less than that observed in the small intestine, thus CDDS protects peptide drugs from hydrolysis, and enzymatic degradation in duodenum and jejunum, and eventually releases the drug into ileum or colon which leads to greater systemic bioavailability. And finally, because the colon has a long residence time which is up to 5 days and is highly responsive to absorption enhancers.

Oral route is the most convenient and preferred route but other routes for CDDS may be used.

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Rectal administration offers the shortest route for targeting drugs to the colon. However, reaching the proximal part of colon via rectal administration is difficult. Rectal administration can also be uncomfortable for patients and compliance may be less than optimal. Drug preparation for intrarectal administration is supplied as solutions, foam, and suppositories. The intrarectal route is used both as a means of systemic dosing and for the delivery of topically active drug to the large intestine. Corticosteroids such as hydrocortisone and prednisolone are administered via the rectum for the treatment of ulcerative colitis. Although these drugs are absorbed from the large bowel, it is generally believed that their efficacy is due mainly to the topical application. The concentration of drug reaching the colon depends on formulation factors, the extent of retrograde spreading and the retention time. Foam and suppositories have been shown to be retained mainly in the rectum and sigmoid colon while enema solutions have a great spreading capacity.

Because of the high water absorption capacity of the colon, the colonic contents are considerably viscous and their mixing is not efficient, thus availability of most drugs to the absorptive membrane is low. The human colon has over 400 distinct species of bacteria as resident flora, a possible population of up to 1010 bacteria per gram of colonic contents. Among the reactions carried out by these gut flora are azo reduction and enzymatic cleavage i.e. glycosides. These metabolic processes may be responsible for the metabolism of many drugs and may

also be applied to colon-targeted delivery of peptide based macromolecules such as insulin by oral administration.

Advantage of colon targeted drug delivery system

1. The colon is rich in lymphoid tissue, uptake of antigens into mast cells of the colonic mucosa produces rapid local production of antibodies and this helps in efficient vaccine delivery.
2. Delivery of the drug in its intact form as close as possible to the target site & reduce conventional dose and frequency.
3. Reduced incidence of adverse side effect.
4. The colon is attracting interest as a site where poorly absorbed drug molecule may have an improved bioavailability. The colon has a longer retention time and appears highly responsive to agents that enhance the absorption of poorly absorbed drugs.
5. Apart from retarding of targeting dosage forms, a reliable colonic drug delivery could also be an important starting position for the colonic absorption of per orally applied, undigested, unchanged and fully active peptide drugs. As the large intestine is relatively free of peptidase such special delivery systems will have a fair chance to get their drug sufficiently absorbed after per oral application.
6. Treatment of local pathologies of the colon such as inflammatory bowel disease (IBD) and colon cancer. Colonic drug delivery can be achieved by oral or rectal administration. With regard to rectal route, suppositories and enema solutions can only offer topical treatment to the sigmoid and descending colon. Therefore, oral administration is preferred.

Limitation and challenges of colon targeted drug delivery

1. As a site for drug delivery, the colon offers a near neutral pH, reduced digestive enzymatic activity, along transit time and increased responsiveness to absorption enhancers; however, the targeting of drugs to the colon is very complicated. Due to its location at the distal portion of the alimentary canal, the colon is particularly difficult to access. In addition, the wide range of pH values and different enzymes present throughout the GI tract, through which the dosage form has to travel before reaching the target site, further complicate the reliability and delivery efficiency.
2. Successful delivery through this site also requires the drug to be in solution form before it arrives in the colon or, alternatively, it should dissolve in the luminal fluids of the colon, but this can be a limiting factor for poorly soluble drugs as the colon is much lower and it is more viscous than in the upper part of the GI tract.
3. In addition, the stability of the drug is also a concern and must be taken into consideration while designing the delivery system. The drug may potentially bind in a nonspecific way to dietary residue, intestinal secretions, mucus or fecal matter.
4. The resident microflora could also affect colonic performance via metabolic degradation of the drug. Lower surface area and relative 'tightness' of the tight junctions in the colon can also restrict drug transport across the mucosa and into the systemic circulation.

MATERIALS AND METHOD

Chemicals

Exenatide was obtained from Sun pharmaceuticals, Na-EDTA (ACS Chemicals), Chitosan (Yarrow chem.), Microcrystalline cellulose (FMC biopolymer), Eudragit S100 (Evonik), Guar gum (Purvi enterprises), Mg-sterate (Purvi enterprises), Aerosil (Purvi enterprises).

Instruments

The following instruments were used for the study: HPLC (Shimadzu (Lc-2010-CHT)), FT-IR (Shimadzu, Japan), Digital Weighing balance (Wensar, DAB-220), Rotary tablet compression machine (Pharma techno), Hardness tester (Monsanto tester), Friability test apparatus (Roche fribilator), Digital pH meter (Thermo Electron Crop, Pune India), Sonicator (Equitron), Dissolution apparatus (Type II paddle).

Fourier Transform Infrared (FTIR)

The compatibility of drug and the excipients was determined by Fourier Transform Infrared spectroscopy (FTIR). The FTIR spectra of pure drug were compared with that of combination of the drug and all the excipients to check for interaction.

Formulation of Core tablet of Exenatide

The formulation was prepared by direct compression method. Weigh Exenatide and all excipients accurately and passed through 60# sieve. Drug and excipients were mixed well and lubricated with talc and aerosil. Weighed quantity of powder mixture was compressed directly on double rotary tablet compression machine by 8/32mm concave punch.

Method for compression coating for Tablets

1. Weigh accurately both ingredients separately and pass these ingredients through 60# sieve.
2. Mix both ingredients in the ratio of 60:40 i.e. 60mg of Eudragit S100 and 40mg of Guar gum.
3. Then for the coating large size of punch was used.
4. Half amount of coating material is placed in the cavity, and then carefully places the core tablet which was formulated in it.
5. After that add the remaining amount of coating material on the upper portion.
6. Finally the tablet is compressed as compression coated tablet in 10mm of punch.

Formulation of batches of Exenatide tablet

Table 1 Formulation of various batches

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Exenatide	3	3	3	3	3	3	3	3	3
Na-EDTA	10	10	10	10	10	10	10	10	10
Chitosan	15	20	25	30	35	40	45	50	55
MCC	73	68	63	58	53	48	43	38	33
Aerosil	1	1	1	1	1	1	1	1	1
Talc	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Formulation of coating material

Table 2

Ingredients	Quantity taken
Eudragit S100	60 mg
Guar Gum	40 mg
Talc	1% w/w

Evaluation

Shape and appearance

Tablets were examined under a lens for the shape of the tablet, and color was observed by keeping the tablets in the light.

Weight variation test

To study weight variation 20 tablets were accurately weighed separately using digital weighing balance and the test was carried out according to the official method. The batch passes the test for weight variation if not more than two of the individual weigh of tablet deviate from the average weight by more than the % shown in the table.

Table 3 Allowable limit for weight variation

Average weight of tablet (X mg)	Percentage deviation
X ≤ 80 mg	10
80 < X 250 mg	7.5
X ≥ 250 mg	5

Hardness test

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. Hardness of tablet was measured by Monsanto hardness tester. It is expressed in kg/cm2.

Friability test

Placed 20 tablets in the Roche friabilitor and rotated for 100 times at 25 rpm and tablets were removed, dusted and weighed again. The %friability was calculated measured by using the formula.

%F = (wo-w/wo)*100
Where,
%F = Friability in %
Wo = Initial weight of the tablet
W = Weight of tablets after test

Drug content

Five tablets were finely powdered quantity equivalent to 3mg of Exenatide taken and dissolved with small amount of 6.8 pH buffer solution into a 100ml of volumetric flask and made up to volume with 6.8 pH buffer solution and mi well thoroughly, 1ml withdrawn and diluted to 100ml with 6.8 pH buffer solution and measured the absorbance at 235nm using HPLC spectrophotometer. The linearity equation obtained from calibration curve was used for the estimation of Exenatide in the tablet formulations.

Dissolution study

Drug release studies were carried out using a dissolution test apparatus (Type2: Paddle apparatus, 50rpm, 37± 0.5°c for 2 hrs in 0.1N HCL (900ml) as the average gastric emptying time is 2hrs. Then the dissolution medium is replaced with pH 7.4 phosphate buffer solution (900ml) and tested for 3hrs as the average intestinal transit time is about 3hrs. Then dissolution is replaced with 6.8 pH buffer solution (900ml). At the end of each time interval 5ml of the samples were withdrawn and 5ml of fresh media is added and the sample is analyzed using HPLC at specific wavelength.

Stability study for an optimized batch

It is vital for formulation development Pharmacist to develop a stable product from formulation as well as regulatory point of view. The regulatory agencies around the globe have rhetoric guidelines of product stability studies. The stability study is performed to check physical and chemical integrity of the formulation.

Storage condition: (5-25°C)
Time period: One month (30 days)
Packing material: Tablets of batch F6 was kept in double plastic zip bags.
Evaluation parameter: Dissolution profile

Short term stability studies on the promising formulation (F6) were carried out by storing tablet in Zip lock bags at refrigerator for 4 weeks. At end of one month, the tablets were examined for in-vitro dissolution profile. Since dissolution study was the evaluating parameter, dissolution profile of the batch under stability study was taken on the day 0 i.e. before the start of study and then again it is taken at the end of the study i.e. after 30 days.

RESULTS AND DISCUSSION

FTIR studies

The results of the FTIR study show that the major peaks present in the pure drug sample were present in the mixture of the drug and the polymers, which indicates that there is no interaction between the drug and the excipients.

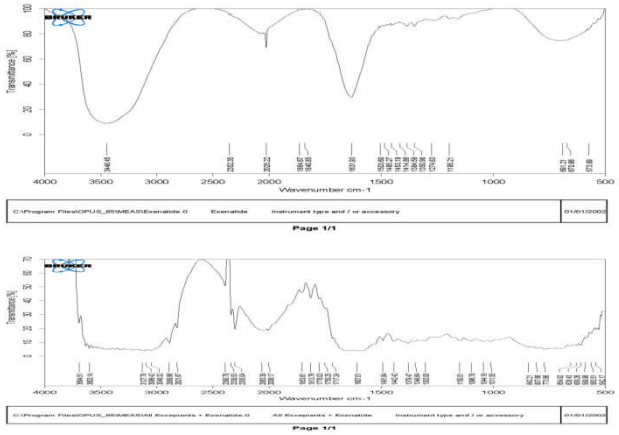


Figure FT-IR of Exenatide + Mixture

Table 4 Comparison between frequency of pure drug and drug + polymer mixture

Sample	-NH (Amine)	C=O (Ketone)	C-H aliphatic	CH2 (Bending)	C-O	C-N
Exenatide	3448	1631	---	1384	1195	1350
Exenatide+ mixture	3694	1607	2889,2821	1379	1150	1348

DISCUSSION

Frequency of the pure drug and after interaction of polymer shown in the table. There was no major change in the frequency occur after interaction of polymer to drug. So the formulation is compatible.

Standard calibration curve of Exenatide

Standard calibration curve of Exenatide in Phosphate buffer

The standard calibration curve of exenatide is shown in figure by using mobile phase for calibration is Phosphate buffer + ACN total run time was 1min/ml for 20 min, retention time was 2.5 min and pH of buffer was 2.5. The data is shown in

table and correlation coefficient (R^2) 0.99 and equation of regressed line is

$y = 0.027x + 0.105$

Table 5 HPLC spectrophotometer readings

Concentration	Mean (SD)	%RSD
10	0.4026±0.00325	0.80823
20	0.65269±0.00287	0.43933
30	0.927±0.003	0.32502
40	1.208±0.00265	0.21936
50	1.5138±0.00171	0.11289
60	1.779±0.00277	0.15598

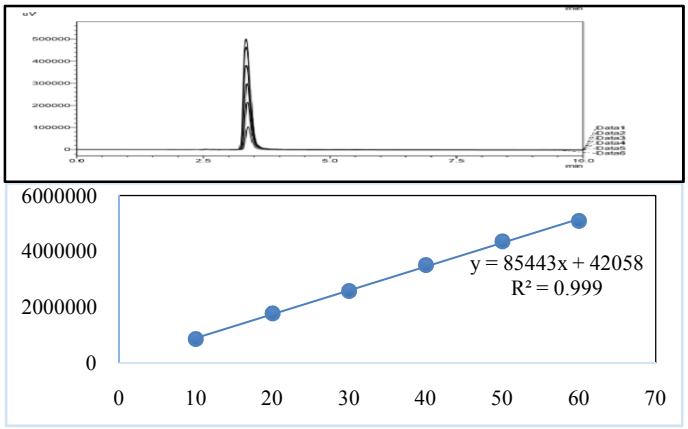


Figure Linearity data of Exenatide

Precompression parameters

Powder mixture of all the formulations were subjected for various precompressional evaluations such as angle of repose, bulk and tapped density, compressibility index and Hausner's ratio. Results of all pre compression parameters are done on drug with other excipient mixture such as Chitosan, Na-EDTA, and Microcrystalline cellulose are shown in table below.

Table 6 Pre-compression Parameters of formulated batch

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Bulk density	0.316	0.717	0.352	0.399	0.678	0.598	0.588	0.507	0.603
Tapped density	0.338	0.853	0.429	0.588	0.779	0.666	0.654	0.649	0.793
Compressibility index	9.15	15.88	16.50	15.33	13.68	11.77	17.36	18.93	16.23
Hausner's ratio	1.068	1.15	1.20	1.52	1.11	1.133	1.22	1.19	1.16
Angle of repose	21.0	25.0	25.0	22.0	20.0	22.0	27.4	26.53	27.0

The results of angle of repose of formulation (<30) indicate good properties of the powder as shown in Table 21. This was further showing low compressibility index values. Generally, compressibility index values up to 18% results in good to excellent flow properties. From above results all the formulation passes the criteria of limits of parameters.

Post-compression parameter of formulated batches

Post-compression parameter contains the result of weight variation, hardness, Thickness, Friability, % drug content, surface appearance, invitro drug release.

In vitro drug release

Table 8 Dissolution profile of formulation batches (F1, F2, and F3)

Medium	Time(hr)	% Drug release		
		F1	F2	F3
0.1 N HCL	0	0.00	0.00	0.00
	1	19.70±0.00	9.33±0.01	7.74±0.0308
	2	31.64±0.053	16.04±0.0245	14.60±0.0308
PHOSPHATE BUFFER 7.4	3	44.82±0.055	51.25±0.7338	22.81±0.2645
	4	63.59±0.305	63.19±0.2516	39.76±0.3789
	5	93.34±0.357	90.5±0.4962	62.0±0.3986
	6			73.12±0.4725
PHOSPHATE BUFFER 6.8	7			83.72±0.5766
	8			
	9			

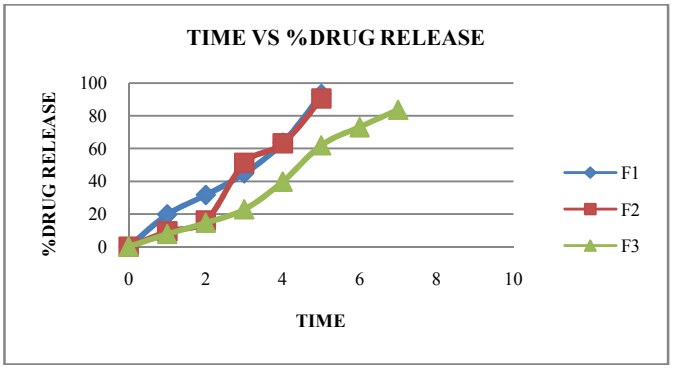


Table 9 Dissolution profile of formulation batches (F4, F5 and F6)

Medium	Time (hr)	% Drug release		
		F4	F5	F6
0.1 N HCL	0	0.00	0.00	0.00
	1	0.00±0.00	0.00±0.00	0.00±0.00
	2	0.00±0.00	0.00±0.00	0.00±0.00
PHOSPHATE BUFFER 7.4	3	8.98±0.2645	6.81±0.456	2.82±0.2775
	4	18.24±0.416	8.75±0.8183	4.06±0.4567
	5	26.79±0.5582	15.0±0.7312	39.57±0.7562
	6	31.35±0.7233	56.29±0.7187	49.66±0.7231
PHOSPHATE BUFFER 6.8	7	48.72±0.7134	63.15±0.013	60.78±0.0145
	8	54.98±0.7184	78.74±0.5403	79.36±0.5523
	9	78.74±0.5400	92.45±0.7720	98.69±0.4582

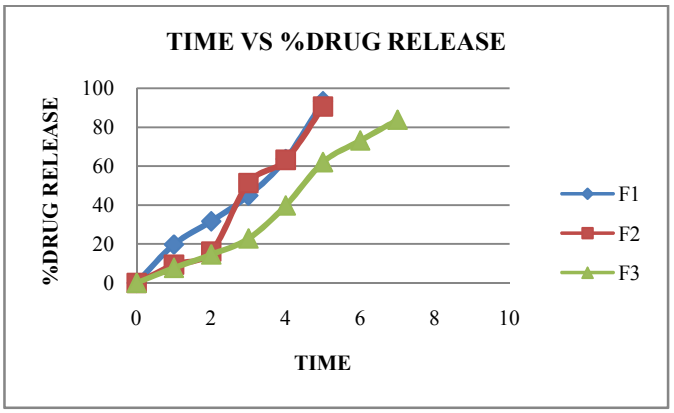
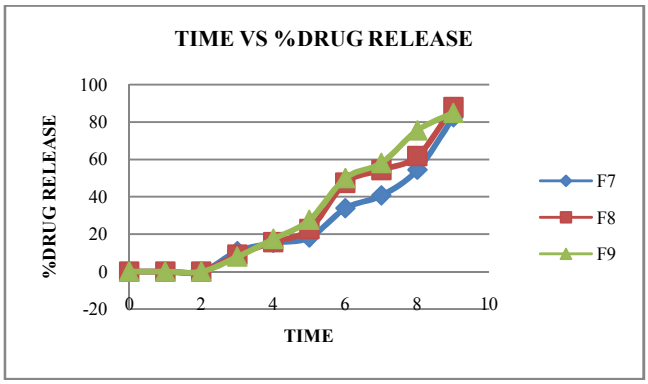


Table 7 Post-compression parameters of formulated batch

Parameter	F1	F2	F3	F4	F5	F6	F7	F8	F9
Surface texture	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth
Weight variation	201±(2.14)	201.58±(4.13)	201.8±(1.13)	200±(3.13)	202.58±(3.13)	201.68±(4.14)	201.68±(4.14)	201.68±(4.0)	201.68±(1.12)
Hardness (kg/cm2)	5.5±(0.018)	5.4±(0.2)	5.46±(0.36)	6.2±(0.13)	6.32±(0.15)	6.5±(0.1)	6.3±(0.122)	6.0±(0.11)	6.4±(0.16)
Friability	0.195±(0.144)	0.299±(0.251)	0.292±(0.188)	0.159±(0.279)	0.258±(0.279)	0.217±(0.33)	0.280±(0.018)	0.233±(0.019)	0.18±(0.016)
Thickness	3.10±(0.50)	3.10±(0.45)	3.10±(0.55)	3.10±(0.48)	3.10±(0.44)	3.10±(0.58)	3.10±(0.45)	3.10±(0.56)	3.10±(0.55)
% Drug content	97.13	96.32	98.80	94.17	97.78	99.50	96.57	97.96	97.87

Table 10 Dissolution profile of Formulation batches (F7, F8 and F9)

Medium	Time(hr)	% Drug Release		
		F7	F8	F9
0.1 N HCL	0	0.00	0.00	0.00
	1	0.00±0.00	0.00±0.00	0.00±0.00
	2	0.00±0.00	0.00±0.00	0.00±0.00
PHOSPHATE BUFFER 7.4	3	10.86±0.2647	9.13±0.5689	7.98±0.7891
	4	15.41±0.3587	15.81±0.0678	17.53±0.2349
	5	18.25±0.4768	22.73±0.16782	27.70±0.7338
	6	33.85±0.7338	47.56±0.2349	50.06±0.0145
PHOSPHATE BUFFER 6.8	7	40.71±0.2564	54.42±0.7891	58.16±0.2647
	8	54.42±0.7189	61.90±0.3450	75.62±0.5766
	9	82.48±0.5679	88.09±0.6748	84.97±0.5582



DISCUSSION

- F1 and F2 shows 93.34 and 90.5 %drug release within 5 hours in Phosphate buffer pH 7.4.
- F3 shows 83 % drug release within 7 hours in Phosphate buffer pH 6.8.
- F4, F5 and F6 gives 78.74, 92.45 and 98.69 % drug release in Phosphate buffer pH 6.8 within 9 hours.
- F7, F8 and F9 gives 82.48, 88.09 and 84.97 % drug release in Phosphate buffer pH 6.8 within 9 hours.
- So from the data of above batches based on drug release profile and physical characteristics with coating for colon targeted drug delivery system F6 batch was optimized.

Stability study of optimized batch

Post compression parameters of optimized batch were calculated on 0 day of the study and after 30 days of study. Results are mentioned in the Table 11. Comparison was done between the 0 day and 30 day results.

Table 11 Post compression parameters of optimized batch at 0 day and at 30 day

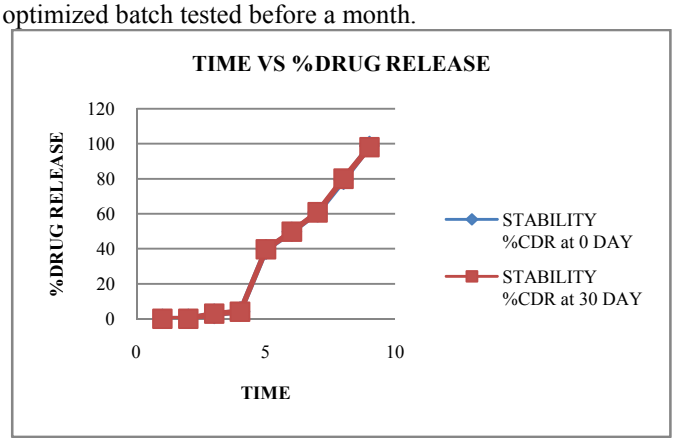
Parameter	At day 0	At day 30
Hardness(kg/cm^2)	6.5	6.5
% Friability	0.28	0.29
% drug content	96.57	96.56

Comparison of in-vitro release profile of batch F6 tablets before and after 30 days stability study

Table 12 %drug release batch at 0 day and 30 day

Time	% drug release at 0 day	% drug release at 30 day
1	0	0
2	0	0
3	2.82	2.84
4	4.06	4.05
5	39.57	39.62
6	49.66	49.70
7	60.78	60.82
8	79.36	80.03
9	98.69	98.00

The percentage of drug release before and after strong was found to be similar. Dissolution profiles before and after storage are nearly overlapping. The change in the drug release pattern i.e. dissolution profile was not significantly different of the tablets tested after 30 days from the dissolution profile of optimized batch tested before a month.



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How to cite this article:

Diksha Pandita *et al* (2018) ' Formulation and Evaluation of Colon Targeted Drug Delivery of Exenatide ', *International Journal of Current Advanced Research,* 07(4), pp. 11381-11386. DOI: http://dx.doi.org/10.24327/ijcar.2018.11386.1968

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