ORIGINAL ARTICLE

Preparation and Evaluation of Celecoxib Polysaccharide Based Matrix Tablets Using NanoParticular Approach

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Abstract

Aim: Celecoxib has a tremendous role in the treatment of colon polyps and Crohn's disease. However, gastric resistant has always been an issue for drug delivery to the colon. Our main intention of this experiment was to prepare and evaluate a formula which could resist gastrointestinal fluid and releases drug content not more than 10% within simulated gastric fluid for 2 h from the time of administration. **Materials and Methods:** In this experiment at first, we prepared Celecoxib nanoparticles using Dyno Mill taking Acconon MC8-2EP as a surfactant and Capmul MCM L-8 as cosurfactant. Freshly prepared Celecoxib nanoparticles were then admixed with Lactopress® anhydrous and using dry granulation technique 10 batches of Celecoxib tablets were formulated by altering various ratios of resistant starch, dextran, and gellan gum. Tablets were prepared using dry granulation technique, where ALTRIN® was considered as a principal binder. **Results and Discussion:** All the pre and post compression parameters were evaluated, and it was found that D-3 batch has legitimate cumulative percentage dissolution profile up to a 24th h (98.12%). Furthermore, similarity and dissimilarity studies were performed against Ortho bed tablet (marketed) and the test optimized formula D-3. The similarity factor (F_2) and difference or dissimilarity factors (F_1) were found to be 60.90 and 10.16, respectively, which is within the specified limits. Finally, as per ICH guideline Q1A (R2) at 40°C ± 2°C/75% RH ± 5% RH accelerated stability studies was performed in the D-3 formulation for 6 months. Stability results were quite satisfactory. **Conclusion:** Hence, it can be concluded that the optimized D-3 batch can be conceded for the pilot scalp.

Key words: Accelerated stability studies, Acconon MC8-2EP, Celecoxib, polysaccharides, similarity factor

INTRODUCTION

In recent years scientists have come up with site-specific targeted drug delivery system. Among which colon specific targeting is one of the challenging approaches. Moreover, in the era of new drug discovery, almost 60% of synthetic drugs has very poor solubility, and rest of the 40% drugs which are in the pipeline of development phase are also faces the same issue.[1] Consequently, lower systematic bioavailability and lower dissolution velocity cause poor membrane permeation and absorption. Hence to succumb all these associated problems of new preclinical drugs, new approaches to drug delivery with improving intrinsic and extrinsic bioavailability is a prerequisite. The biggest challenges scientists are witnessing with BCS Class-II (permeable and less soluble), and BCS Class-IV (less permeable and insoluble) is drug delivery to the site and drug administrative complication with patient compliances.[2] Recently scientist has triggered to developed formulations with the nanoparticular approach, which has several advantages like higher surface area, which actually satisfied Noyes-Whitney hypothesis of effective drug absorption. Further, nanoparticular formulations possessed 10-1000 nm ranged particles, which could lead to improving solubility, dissolution velocity, membrane permeability, and bioavailability.[3,4] In this experiment, the main intention was to prepare suitable nanoparticles of Celecoxib using Dyno mill and incorporate this nano-sized particle of Celecoxib with suitable polysaccharides such as resistant starch, dextran,[5] and gellan gum to produce

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dry granulated effective tablets for colon-specific targeting. Celecoxib, a BCS-II drug is using in colon polyps and Crohn's disease. The concept of using polysaccharides for colon targeted drug delivery is to resist gastrointestinal tract hostile condition and degrades in the presence of colonic bacteria's; hence it can be used for rate limiting step for drug release. After admixing prepared nanoparticle of Celecoxib with adequate quantities of excipients for tablet preparation, various micrometric studies such as angle of repose, bulk density, tap density, Carr's index, Hausner ratio (HR) ratio, drug content, and porosity was performed. Further, infrared (IR) and differential scanning calorimetry (DSC) studies were performed to characterized possible interaction within the drug excipient and melting-crystallization endothermic deflection of the drug in formulations. Almost all the post-compression parameter was evaluated and similarity and dissimilarity factor was calculated against of marketed matrix tablet for a better understanding of dissolution profile of the prepared optimized formulation. Finally, as per ICH guideline, 6-month stability studies was performed.[6]

MATERIALS AND METHODS

Materials for the preparation of nanoparticles and matrix tablet of Celecoxib

Celecoxib (drug) was gifted by Prudence Pharma Chem-Ankleshwar, Gujarat. Hydroxypropyl cellulose L grade (Nisso America Inc.) (HPC-L) was procured from Hercules, USA. Acconon MC8-2EP and Campul MCM C-8 were a gift sample from ABITEC Corporation, USA. Resistant starch, dextran, and gellan gum were purchased from Triveni Interchem Pvt. Ltd. Vapi. MALTRIN® was purchased from Vijay Enterprises Maharashtra, India. Lactopress® anhydrous was purchase from Indchem International, Mumbai, Maharashtra. Crospovidone-PPXL10 grade was purchased from IPS, USA. Magnesium stearate; Aerosil-200 was purchased from Balaji Drugs, Gujarat. MCC - Pharmacel® 101 was a gift sample from DFE Pharma-Germany.

Method - Using Dyno Mill preparation of Celecoxib nanoparticles

Dyno-Mill has a significant role in the small scale of nanoparticles development. During the preparation of nanoparticles, HPC-L was used as a stabilizer, were else Acconon MC8-2EP used as a surfactant and Capmul MCM L-8 as cosurfactant. The dispersion of stabilizer, surfactant, and cosurfactant was prepared using double deionized water to produce 40% dispersion. To the dispersion add a measured quantity of Celecoxib drug and homogenized at 2400 rpm for 45 min. Using zirconium beads (grinding media) freshly prepared nanosuspension was milled in Dyno Mill KDLA. The total composition of the contents of preparation was reported in Table 1.

Table 1: Ingredients of nanosuspension during Celecoxib nanoparticle preparation

S.No.	Ingredients name	Quantity in g	Percentage
1	Celecoxib	1 g (100 m for each batch)	0.125
2	HPC-L	36	4.5
3	Acconon MC8-2EP	1.5	0.18
4	Capmul MCM L-8	1.5	0.18
5	Deionized water	760	95
Total		800	100

HPC-L: Hydroxypropyl cellulose L grade (Nisso America Inc.)

Conversion of nanosuspension into nanoparticles using spray drying technique

Almost 770 g of nanosuspension was charged in BUCHI Mini spray dryer, maintaining inlet temperature at 200°C, outlet temperature at 45°C and nitrogen gas pressure up to 24 psi. At list, 250 g of deionized water was extra charged in the processing suspension for decreasing viscosity of the suspension and easy passage through the spray nozzle. The spray drying was continued up to 5 h. After 5 h of drying % yield and % assay was calculated.

Fabrication of Celecoxib nanoparticles and dry granulation technique

Using dried Celecoxib nanoparticles and suitable polysaccharides such as resistant starch, dextran, and gellan gum suitable tablets were manufactured. The binder used for this proceedings were MALTRIN®; a maltodextrins and corn syrup solid derivatives. The accurately measured quantity of Celecoxib nanoparticle (102.5 mg of the nanoparticle is equivalent to 100 mg of Celecoxib salt) and diluent Lactopress® anhydrous was mixed together in geometrical dilution and pass through mesh number #60. Rest of the excipients, except magnesium stearate and aerosil-200, were mixed and pass through mesh number #40. Now, Celecoxib nanoparticular lactose bland and rest of the excipient was mixed together. Previously meshed (#60) lubricants magnesium stearate and aerosil-200 was incorporated into freshly prepared bland and lubricated for 10 min using polyethylene bags in one direction. Based on the different concentration of polysaccharides total 10 batches was formulated. Tablets were manufactured using 10 stations rotary tablet punching machine (Riddhi Pharma Machinery Limited, Mumbai).

Similarity and dissimilarity study

This approach uses difference factor (F_1) and similarity factor (F_2) to compare the dissolution profile of optimized D-3

profile and along with marketed product 100 mg Ortho bed tablet (Abbott Healthcare Private Limited). The difference factor (F_1) calculates the percentage (%) difference the two curves at each time point and is a measurement of the relative error between the two curves:

$$F_1 = \{[\sum_{t=1}^{n} | R_t - T_1 |] / [\sum_{t=1}^{n} R_t]\} \times 100 \quad (1)$$

Where, n = Number of time point, R_t = Dissolution value of the reference batch at time t, T_t = Dissolution value of the test batch at time t.

Similarity factor (F_2) is a logarithmic reciprocal sequence root transformation of the sum of squared error and is the measurement of the similarity in the percentage (%) dissolution between the curves.

$$F_2 = 50.\log\{[1 + (1/n)\sum_{t=1}^{n} |R_t - T_t|^2]^{-0.5} \times 100\} \quad (2)$$

To calculate the difference and the similarity factor, first, the dissolution profile should be done. The difference factor (F_1) and similarity factor (F_2) can be calculated using the mean dissolution value from both curves at each time interval. If the value is more than 50 it is similar (F_2). If the value is <50 it is dissimilar or difference (F_1).[7]

Stability studies and report

Stability studies were performed using stability chamber (Eye Instruments Pvt. Ltd., Ahmedabad) on D-3 batches tablets for 6 months. The stability parameters such as hardness, drug content, *in vitro* dissolution, friability, disintegration time, and matrix integrity, were recorded. The results were satisfactory up to a 6th month.

RESULTS AND DISCUSSION

Initially prepared nanoparticles maintained 0.087 µm mean particular diameter. The stabilizer HPC-L gave significant results after post milling particular diameter and overall free flowing nanoparticles without agglomerates [Table 1]. During processing's, IR and DSC studies were performed. Which suggested that no possible chemical interaction took place within Celecoxib, resistant starch, dextran, and gellan gum. No effective changes were seen in Celecoxib-crystallization endotherm and melting endotherm. Based on IR and DSC studies 10 formulas had been designed for this experiment [Table 2]. Pre-compression parameters suggested that blend maintains good flow ability, the limited angle of repose, limited bulk, and tap density, effective HR, and less percentage of loss on drying [Table 3]. Almost all the formulations post-compression parameters were checked. As per USP standards

Table 2: Designed formula for all the 10 batches of Celecoxib tablets

Batch Number	Spray dried Celecoxib powder (102.5)+Lactopress® anhydrous (104.5) mg	MALTRIN®	Gellan gum	Dextran	Resistant starch	Crospovidone USP-NF-PPXL-10	MCC (Pharmacel® 101)	Magnesium stearate	Aerosil-200	Per tablet weight (mg)
M-1	207	10.35	-	-	-	40	282.65	6	4	550
G-1	207	10.35	25	-	-	40	257.65	6	4	550
G-2	207	10.35	50	-	-	40	232.65	6	4	550
G-3	207	10.35	75	-	-	40	207.65	6	4	550
D-1	207	10.35	-	150	-	40	132.65	6	4	550
D-2	207	10.35	-	175	-	40	107.65	6	4	550
D-3	207	10.35	-	200	-	40	82.65	6	4	550
RS-1	207	10.35	-	-	200	40	82.65	6	4	550
RS-2	207	10.35	-	-	220	40	62.65	6	4	550
RS-3	207	10.35	-	-	240	40	42.65	6	4	550

Table 3: Pre-compassion parameters and evaluation results of formulations bland

Batch number	Angle of repose (°)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index (%)	HR	Loss on drying (%)
M-1	28.89	0.361	0.412	12.37	1.14	1.21
G-1	26.16	0.345	0.398	13.31	1.15	0.36
G-2	31.11	0.561	0.634	11.51	1.13	1.67
G-3	34.71	0.710	0.823	13.73	1.15	2.19
D-1	22.81	0.268	0.342	21.63	1.27	1.63
D-2	25.82	0.278	0.376	26.06	1.35	2.15
D-3	28.91	0.348	0.489	28.83	1.40	0.98
RS-1	26.81	0.651	0.782	16.75	1.20	1.56
RS-2	27.14	0.281	0.378	25.66	1.34	1.22
RS-3	26.09	0.437	0.578	24.39	1.32	2.07

HR: Hausner ratio

Table 4: Evaluation results of post-compression parameters of all the formative batches

Batch number	Hardness (Kph)	Thickness (mm)	Diameter (mm)	Weight Variation [mg]	Friability [%]	Drug content (%)	Disintegration time (min)
M-1	8.25±0.92	4.96±0.91	10.04±0.81	554.78±0.01	0.672	92.89	3.12
G-1	8.13±0.87	4.81±0.26	10.12±0.09	551.56±0.09	0.781	94.91	2.16
G-2	9.78±0.02	4.97±1.76	10.63±0.72	550.81±0.03	0.456	92.28	3.19
G-3	10.86±0.78	4.82±0.25	10.04±0.83	550.17±0.12	0.762	87.91	5.33
D-1	6.81±0.12	4.87±0.08	10.62±0.97	551.91±0.04	0.561	98.81	2.13
D-2	7.22±0.27	4.97±0.02	10.08±0.03	550.13±0.82	0.812	93.91	3.42
D-3	9.27±0.22	4.88±0.07	10.26±0.91	550.29±0.92	0.672	88.91	4.05
RS-1	6.81±0.49	5.01±0.90	10.22±0.02	552.82±0.04	0.627	96.92	2.08
RS-2	7.81±0.71	4.87±0.81	10.09±0.92	550.18±0.07	0.689	92.15	3.57
RS-3	09.19±0.56	4.93±1.08	10.26±0.61	550.81±0.03	0.712	88.71	4.18

Table 5: *In vitro* cumulative drug release study for M-1 formulation

Percentage cumulative drug release (%)	
Time in hour	**Formulation M-1**
SGF	
1	7.85
2	18.17
SIF	
3	32.18
4	39.71
5	56.19
6	67.18
SCF	
7	81.60
8	99.82

SGF: Simulated gastric fluid, SIF: Simulated intestinal fluid, SCF: Stimulated colonic fluid

drug content, hardness, thinness, diameter, disintegration time, weight variation was measured and tabulated [Table 4]. The prepared formulation *in vitro* dissolution studies were performed using three different solutions; simulated gastric fluid, intestinal fluid, and colonic fluid (TS, Ricca Chemical). The results were concluded with splendid facts [Tables 5-8], M-1 formulation consisting of only MALTRIN® binder and maximum MCC achieved poor dissolution profile. After an 8th h, the formulation has almost released 99.83% of Celecoxib, which was not acceptable. Formulation G-1 to G-3 also has a problem that is uneven dissolution profile. An increase concentration of gellan gum leads to maximize dissolution in the upper stomach (range 26.78-32.18%) which was above the limit. This dissolution enhancement of G-1 to G-3 formulations caused due to the higher solubility of gellan gum with the gastric juice and hydrochloric acid. Moreover, up to 98.11% (G-3), cumulative drug release was observed at colonic fluid after 12th h dissolution. With this tangible evidence, one can conclude that M-1 and G-1, G-2, G-3 are not suitable for colon-specific targeting. On the other hand,

Table 6: *In vitro* cumulative drug release studies for formulation G-1, G-2, and G-3

	Percentage cumulative drug release (%)		
Time in hour	Formulation G-1	Formulation G-2	Formulation G-3
SGF			
1	14.48	17.14	21.39
2	26.78	29.17	32.18
SIF			
3	32.81	35.19	35.15
4	39.03	41.29	40.22
5	45.72	47.29	46.07
6	52.19	53.91	52.19
SCF			
7	64.81	67.17	60.11
8	72.79	73.11	67.09
9	79.22	81.18	74.83
10	85.27	86.81	81.21
11	91.39	93.92	91.62
12	97.86	98.05	98.11

SGF: Simulated gastric fluid, SIF: Simulated intestinal fluid, SCF: Stimulated colonic fluid

Table 7: *In vitro* cumulative drug release studies for formulation D-1 to D-3

	Percentage cumulative drug release (%)		
Time in hour	Formulation D-1	Formulation D-2	Formulation D-3
SGF			
1	4.81	2.11	3.86
2	9.18	8.61	7.87
SIF			
3	14.87	12.69	11.82
4	17.98	15.81	15.39
5	23.11	19.09	19.17
6	28.16	22.81	24.16
SCF			
7	43.16	37.11	36.89
8	50.13	42.19	43.19
9	58.43	49.17	50.13
10	60.19	57.91	56.17
11	67.71	63.17	63.11
12	74.05	70.13	70.57
14	81.19	76.11	76.13
16	87.19	84.91	85.88
20	94.18	90.15	93.15
24	105.81	102.94	98.12

SGF: Simulated gastric fluid, SIF: Simulated intestinal fluid, SCF: Stimulated colonic fluid

Table 8: *In vitro* cumulative drug release studies for formulation RS-1 to RS-3

	Percentage cumulative drug release (%)		
Time in hour	Formulation RS-1	Formulation RS-2	Formulation RS-3
SGF			
1	7.18	07.71	06.18
2	15.94	16.66	11.90
SIF			
3	32.17	33.81	35.11
4	40.18	42.13	39.18
5	48.91	48.18	45.11
6	56.28	59.02	58.18
SCF			
7	73.19	70.16	72.68
8	75.10	75.10	77.88
9	80.17	79.91	81.45
10	85.78	84.11	84.82
11	90.99	87.91	89.18
12	94.18	93.95	93.81
14	98.17	97.19	97.88
16	108.16	106.89	102.87

SGF: Simulated gastric fluid, SIF: Simulated intestinal fluid, SCF: Stimulated colonic fluid

D-3 formulation possessed 98.12% cumulative drug release after 24 h of dissolution and has only 7.87% of cumulative drug release at gastric environment after 2 h of dissolution, indicating best formulation emerged during dissolution. While RS-1 to RS-3 dissolution, it was recognized that resistant starch provides good dissolution profile, but it releases maximum drug (102.87% for RS-3) only up to a 16th h [Figure 1]. The combination of MALTRIN® and dextran formulations (D-1 to D-3) were effective because dextran has maximum branched glucan polysaccharide made up of several glucose chains (α-D glucose molecule), due to which it releases the drug diffusively and has less effect on the upper stomach. Significantly colonic surface bacteria's produces dextranase enzymes, which cleaves dextran contents of the formulation (D-1 to D-2) effectively and slowly, the reconsolidating extended release of those formulations. After dissolution studies, similarity and dissimilarity or difference factors were determined [Table 9]. The Ortho bed tablet was taken as a reference sample (R_t), and optimized D-3 was taken as a test sample (T_t). The similarity and difference factor was found to be 60.907 and 10.1651, which is within the specified limits [Figure 2]. At final stage accelerated stability studies on D-3 formulation was performed as per ICH guideline Q1A (R2) at 40°C ± 2°C/75% RH ± 5% RH for 6 months. All the evaluation parameters during accelerated conditions were performed for 6 month, and results were satisfactory, except after 6 months of stability studies partial erosion were

Table 9: Similarity and difference factor study results for Ortho bed tablet (marketed) and the test optimized formula D-3

Time in hour	%CDR of Ortho bed tablet (Reference sample)-R_t	%CDR of test sample, D-3-T_t	R_t-T_t	$(R_t-T_t)^2$	$\lvert R_t-T_t\rvert$
0	0	0	0	0	0
1	5.04	3.86	1.18	1.3924	1.18
2	9.57	7.87	1.7	2.89	1.7
3	13.04	11.82	1.22	1.4884	1.22
4	19.33	15.39	3.94	15.5236	3.94
5	26.95	19.17	7.78	60.5284	7.78
6	33.78	24.16	9.62	92.5444	9.62
7	40.81	36.89	3.92	15.3664	3.92
8	48.11	43.19	4.92	24.2064	4.92
9	55.63	50.13	5.5	30.25	5.5
10	60.33	56.17	4.16	17.3056	4.16
11	67.27	63.11	4.16	17.3056	4.16
12	76.34	70.57	5.77	33.2929	5.77
14	83.91	76.13	7.78	60.5284	7.78
16	93.88	85.88	8	64	8
20	99.12	93.15	5.97	35.6409	5.97
24	108	98.12	9.88	97.6144	9.88
N=16	Summation of the R_t=841.11	Difference factor (0-15) F_1=10.1651		Summation of $(R_t-T_t)^2$=569.8778	Sum of$\lvert R_t-T_t\rvert$=85.5
Similarity factor (50-100), F_2=60.9070					

CDR: Cumulative drug release

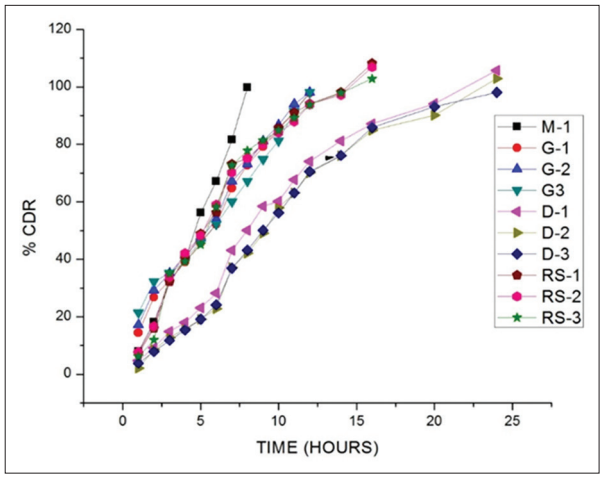

Figure 1: Percentage cumulative drug release of prepared 10 Celecoxib matrix tablet

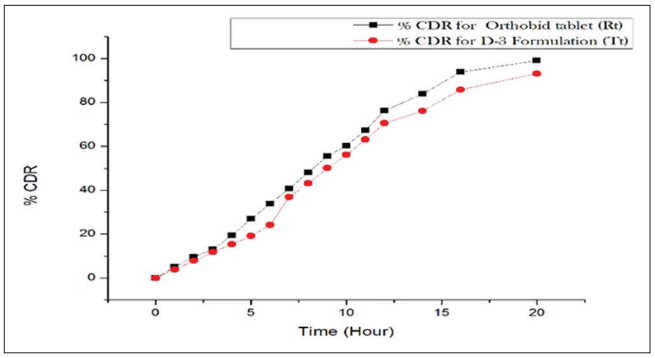

Figure 2: Percentage cumulative drug release of Ortho Bed tablet and optimized D-3 formulation during similarity and dissimilarity study design

seen from the tablet surface matrix, and excessive dissolution release (105.09%) profile was observed after 24 h [Tables 10 and 11; Figure 3]. Hence, it can be concluded that prepared formulation maintained its integrity and can be considered for pilot seal up.

CONCLUSION

It had been a novel and challenging approach to preparing nanoparticle-based Celecoxib matrix tablets using dry granulation technique. Since the formulations were specifically designed for colon targeting, hence various polysaccharides were used to formulate matrix tablets.

Table 10: Accelerated stability studies on D-3 formulation, as per ICH guideline Q1A (R^2) at 40°C±2°C/75% RH±5% RH for 6 month

Stability parameters	1st month	2nd month	3rd month	4th month	5th month	6th month
Hardness (kph)	9.20,0.92	9.02,0.29	8.98,0.12	8.11,0.29	7.82,0.11	7.12,0.53
Drug content (%)	87.84	87.42	86.81	86.06	85.91	85.49
Friability (%)	0.670	0.762	0.826	0.862	0.890	0.956
Disintegration time (minutes)	5.16	5.34	5.28	5.32	4.29	4.08
Matrix integrity	Good	Good	Faire	Little moist	Partial erodible	Partial erodible

Table 11: As per ICH guideline Q1A (R^2) *in vitro* dissolution studies for D-3 formulation

Time in hour	% CDR at 1st month	% CDR at 2nd month	% CDR at 3rd month	% CDR at 4th month	% CDR at 5th month	% CDR at 6th month
0	0	0	0	0	0	0
1	3.21	4.13	4.48	4.98	5.21	5.88
2	7.92	8.19	8.43	8.82	9.01	9.42
3	10.31	11.44	12.64	12.98	13.43	13.68
4	16.19	17.11	17.38	17.96	18.56	18.96
5	20.91	21.83	22.17	22.97	23.72	24.71
6	25.08	26.11	26.98	27.26	27.92	28.19
7	38.33	39.46	40.91	41.75	42.18	43.61
8	49.21	50.34	51.41	52.17	53.02	53.81
9	52.88	53.16	54.81	55.03	55.78	56.18
10	57.11	58.27	59.28	60.26	60.97	61.81
11	65.61	66.51	67.11	68.26	69.28	70.32
12	74.11	75.11	76.62	77.46	79.17	80.62
14	77.19	78.28	80.34	82.62	83.97	85.61
16	87.11	89.21	91.63	93.82	95.08	96.04
20	95.11	96.48	97.72	98.19	99.63	101.73
24	98.98	99.54	99.96	100.34	104.11	105.09

CDR: Cumulative drug release

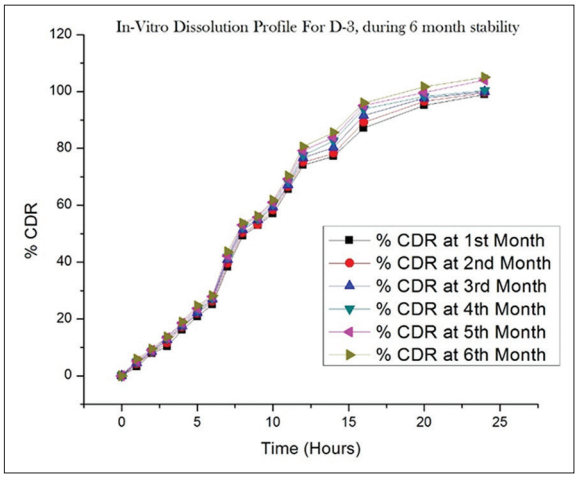

Figure 3: Dissolution profile of optimized D-3 formulation during 6 months accelerated stability studies

Among which dextran was found to have very promising as far as the simulated colonic mucosal resistance profile was concerned. From the stability profile, it can be concluded that pre-optimized D-3 formulation maintains its physical stability almost up to 6 months. Further, *in vivo* research need to be a warrant for a better understanding of dosage form behavior in bioavailability and dissolution profile.

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