Original Article

Preparation and evaluation of rofecoxib polysaccharide-based matrix tablets using nanoparticular approach

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ABSTRACT

Rofecoxib 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. The main intention of this research was to prepare and evaluate an optimized formulation that could resist gastrointestinal fluid and releases drug content not more than 10% within simulated gastric fluid for 2 h from the time of administration. Rofecoxib nanoparticles were prepared using Dyno mill, considering Acconon MC8-2EP as a surfactant and Capmul MCM L-8 as co-surfactant. Freshly prepared rofecoxib nanoparticles were then admixed with Lactopress® anhydrous and using dry granulation technique ten batches of rofecoxib tablets were formulated by altering various ratios of resistant starch, dextran, and gellan gum. Tablets were prepared using a dry granulation technique, where ALTRIN® was considered as a principal binder. All the pre- and post-compression parameters were evaluated and it was found that D-3 batch has a legitimate cumulative percentage dissolution profile, i.e., 98.12% at 24th h. Furthermore, similarity and dissimilarity studies were performed against Orthobid tablets (marketed) and with optimized formulation (D-3). The similarity factor (F2) and difference or dissimilarity factors (F1) were found to be 60.90 and 10.16, respectively, which is within the specified limits. Finally, as per ICH (Q1A (R2) guideline, accelerated stability studies were performed in the D-3 formulation for 6 months. Stability results were reliable and trustworthy for considering as a stable formulation. Hence, it can be concluded that the optimized D-3 batch can be conceded for the pilot scalp.

Keywords: Rofecoxib, similarity factor, polysaccharides, Acconon MC8-2EP, accelerated stability studies

INTRODUCTION

Site-specific drug delivery system is the new dimension, where scientists are more interested to work in. Among all the site-specific drug delivery systems, colon specific targeting is one of the most challenging approach to develop. The existing most drugs are having only 60% systematic bioavailability due to their poor solubility in tissue fluid and rest 40% are in developing pipeline. Mostly, due to poor solubility and bioavailability, drugs are becoming more impermeable in blood vessel.[1-3] Consequently, lower systematic bioavailability and lower dissolution velocity cause poor membrane permeation and absorption.[4] Hence, to succumb all such associated problems of new preclinical drugs, new approaches to drug delivery with improving intrinsic and extrinsic bioavailability are prerequisite.[5] The principal challenges scientists are facing 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.[6] 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.[7] Further, nanoparticular formulations possessed 10–1000 nm ranged particles, which could lead to improving solubility, dissolution velocity, membrane permeability, and bioavailability. In this experiment, the main intention was to prepare

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suitable nanoparticles of rofecoxib using Dyno mill[8] and incorporate these nano-sized particles of rofecoxib with suitable polysaccharides such as resistant starch, dextran, and gellan gum to produce dry granulated effective tablets for colon-specific targeting. Rofecoxib, a BCS-II drug, is used in colon polyps and Crohn's disease.[9]The concept of using polysaccharides for colon-targeted drug delivery was to resist gastrointestinal tract hostile conditions and to felicitate colonic bacterial degradation. Hence, it can be used for the rate-limiting step for drug release. After admixing prepared nanoparticle of rofecoxib with adequate quantities of excipients for tablet preparation, various micrometric studies such as angle of repose, bulk density, tap density, Carr's index, HR ratio, drug content, and porosity were performed. [10] Almost all the post-compression parameter was evaluated and similarity and dissimilarity factor were calculated against of marketed matrix tablet for a better understanding of dissolution profiling of the prepared optimized formulation. Finally, as per ICH guideline, 6-month stability studies were performed.

MATERIAL AND METHODS

Materials for the preparation of nanoparticles and matrix tablet of rofecoxib

Rofecoxib (drug) was gifted by Prudence Pharma Chem-Ankleshwar, Gujarat. Hydroxypropyl cellulose (HPC-L) was procured from Hercules, U.S.A. Acconon MC8-2EP and Campul MCM C-8 were a gift sample from ABITEC Corporation, U.S.A. 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. Cross povidone-PPXL10 grade was purchased from IPS, U.S.A. Magnesium stearate, Aerosil-200, was purchased from Balaji drugs, Gujarat. Microcrystalline cellulose (MCC) – Pharmacel® 101 was a gift sample from DFE Pharma-Germany.

Method using dyno mill preparation of rofecoxib nanoparticles

Dyno mill has a significant role in the small scale of nanoparticles development.[11] During the preparation of nanoparticles, HPC-L was used as a stabilizer, was else Acconon MC8-2EP used as a surfactant and Capmul MCM L-8 as co-surfactant. 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 rofecoxib 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 the following Table 1.

Conversion of nanosuspension into nanoparticles using spray drying technique

Almost 770 g of nanosuspension was charged in BUCHI mini spray dryer,[12] 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.

Table 1: Ingredients of nanosuspension during rofecoxib nanoparticle preparation

Ingredients name	Quantity in g	Percentage
Rofecoxib	1 g (100 mg for each batch)	0.125
HPC-L	36	4.5
Acconon MC8-2EP	1.5	0.18
Capmul MCM L-8	1.5	0.18
Deionized water	760	95
Total	800	100

Fabrication of rofecoxib nanoparticles and dry granulation technique

Using dried rofecoxib nanoparticles and suitable polysaccharides such as resistant starch, dextran, and gellan gum suitable tablets were manufactured. The binder used for this proceeding was MALTRIN®; a maltodextrins and corn syrup solid derivatives.[13] The accurately measured quantity of rofecoxib nanoparticle (102.5 mg of the nanoparticle is equivalent to 100 mg of rofecoxib salt) and diluent Lactopress® anhydrous was mixed together in geometrical dilution and pass through mesh number #60. The rest of the excipients, except magnesium stearate and aerosil-200, were mixed and passed through mesh number # 40. Now, rofecoxib 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 concentrations of polysaccharides total of 10 batches were formulated. Tablets were manufactured using 10 stations rotary tablet punching machine (Riddhi Pharma Machinery Limited, Mumbai).

Similarity and dissimilarity stud

This approach uses difference factor (F_1) and similarity factor (F_2)[14] to compare the dissolution profile of optimized D-3 profile and along with marketed product 100 mg Orthobid tablet (Abbott Healthcare Private Limited). The difference factor (F1) calculates the percentage (%) difference the two curves at each time point and is a measurement of the relative error between the two curves:

$$F1 = \{[\sum_{t=1}^{n} |Rt - T1|] / [\sum_{t=1}^{n} Rt]\} \times 100 \quad (1)$$

Where n=number of time point, Rt=dissolution value of the reference batch at time t.

Tt= dissolution value of the test batch at time t.

Similarity factor (F2) 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 curve.

$$F2 = 50.\log \{[1 + (1/n) \sum_{t=1}^{n} |Rt - Tt|^2]^{-0.5} \times 100 \quad (1)$$

To calculate the difference and the similarity factor, first, the dissolution profile should be done. The difference factor (F1) and similarity factor (F2) 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 (F2). If the value is less than 50, it is dissimilar or difference (F1).

Stability studies and report

Stability studies were performed using the 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 the 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 a particular diameter and overall free-flowing nanoparticles without agglomerates [Table 1]. During processing, infrared and differential scanning calorimetry studies were performed. This suggested that no possible chemical interaction took place within rofecoxib, resistant starch, dextran, gellan gum. No effective changes were seen in rofecoxib-crystallization endotherm and melting endotherm. Based on further studies, ten formulas had been designed for this experiment [Table 2]. Pre-compression parameters suggested that blend maintains good flowability, the limited angle of repose, limited bulk, and tap density, effective Hausner ratio and less percentage of loss on drying [Table 3]. Almost all the formulations post-compression parameters were checked. As per USP standards, 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) [Figure 1]. The results were concluded

Table 2: Designed formula for all the ten batches of rofecoxib tablets

Batch number	Spray dried rofecoxib powder (102.5) + Lactopress® anhydrous (104.5) mg	MALTRIN®	Gellan gum	Dextran	Resistant starch	Crospovidone USP-NF-PPXL-10	Microcrystalline cellulose (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 (%)	Hausner ratio	Loss on drying (%)
M-1	28.89±0.01	0.361±0.04	0.412±0.02	12.37±1.05	1.14±0.30	1.21±0.04
G-1	26.16±0.31	0.345±0.04	0.398±0.04	13.31±1.11	1.15±0.03	0.36±0.01
G-2	31.11±0.12	0.561±0.03	0.634±0.06	11.51±1.45	1.13±0.13	1.67±0.05
G-3	34.71±0.03	0.710±0.02	0.823±0.04	13.73±1.73	1.15±0.23	2.19±0.02
D-1	22.81±0.02	0.268±0.08	0.342±0.01	21.63±0.45	1.27±0.41	1.63±0.05
D-2	25.82±0.02	0.278±0.03	0.376±0.03	26.06±0.67	1.35±0.23	2.15±0.56
D-3	28.91±0.02	0.348±0.07	0.489±0.05	28.83±1.24	1.40±0.25	0.98±0.51
RS-1	26.81±0.03	0.651±0.11	0.782±0.12	16.75±0.65	1.20±0.38	1.56±0.05
RS-2	27.14±0.05	0.281±0.02	0.378±0.14	25.66±0.11	1.34±0.28	1.22±0.07
RS-3	26.09±0.03	0.437±0.05	0.578±0.04	24.39±0.34	1.32±0.45	2.07±0.05

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

Batch number	Hardness (Kph)	Thickness (mm)	Diameter (mm)	Weight variation	Friability	Drug content (%)	Disintegration time (minutes)
M-1	8.25±0.92	4.96±0.91	10.04±0.81	554.78±3.11	0.672±0.03	92.89±1.04	3.12±0.13
G-1	8.13±0.87	4.81±0.26	10.12±0.09	551.56±1.20	0.781±0.01	94.91±2.07	2.16±0.45
G-2	9.78±0.02	4.97±1.76	10.63±0.72	550.81±1.33	0.456±0.06	92.28±1.34	3.19±1.04
G-3	10.86±0.78	4.82±0.25	10.04±0.83	550.17±1.32	0.762±0.04	87.91±1.34	5.33±0.03
D-1	6.81±0.12	4.87±0.08	10.62±0.97	551.91±1.44	0.561±0.05	98.81±2.14	2.13±0.34
D-2	7.22±0.27	4.97±0.02	10.08±0.03	550.13±1.32	0.812±0.02	93.91±1.46	3.42±0.52
D-3	9.27±0.22	4.88±0.07	10.26±0.91	550.29±1.42	0.672±0.03	88.91±1.34	4.05±0.34
RS-1	6.81±0.49	5.01±0.90	10.22±0.02	552.82±1.24	0.627±0.04	96.92±1.45	2.08±0.43
RS-2	7.81±0.71	4.87±0.81	10.09±0.92	550.18±1.37	0.689±0.04	92.15±2.85	3.57±0.17
RS-3	09.19±0.56	4.93±1.08	10.26±0.61	550.81±1.33	0.712±0.01	88.71±2.67	4.18±0.10

with impressive facts [Tables 5-9]. 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 rofecoxib, which was not acceptable. Formulation G-1 to G-3 also has a problem that is an uneven dissolution profile. An increased concentration of gellan gum leads to maximize dissolution in the upper stomach (range 26.78–32.18%) which was above the limit.

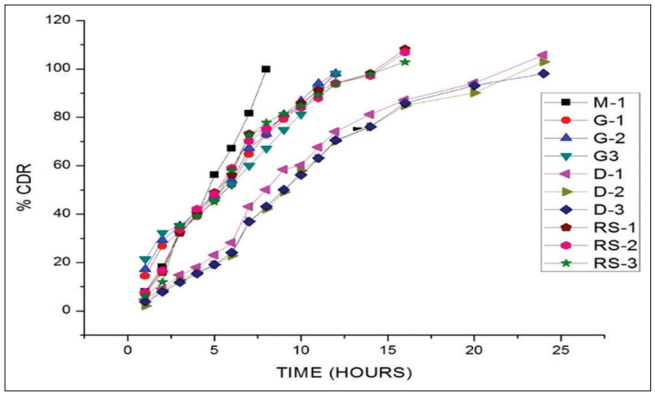

Figure 1: Percentage cumulative drug release of prepared 10 rofecoxib matrix tablet

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

Percentage cumulative drug release (%)	
Time in hour	**Formulation M-1**
Simulated gastric fluid	
1	7.85±0.03
2	18.17±0.12
Simulated intestinal fluid	
3	32.18±1.45
4	39.71±0.63
5	56.19±1.45
6	67.18±1.24
Simulated colonic fluid	
7	81.60±0.61
8	99.82±0.41

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**
Simulated gastric fluid			
1	14.48±1.34	17.14±1.53	21.39±0.02
2	26.78±1.44	29.17±1.22	32.18±0.45
Simulated intestinal fluid			
3	32.81±1.23	35.19±1.56	35.15±0.34
4	39.03±1.44	41.29±0.24	40.22±0.38
5	45.72±1.47	47.29±0.45	46.07±0.31
6	52.19±1.04	53.91±0.34	52.19±0.11
Simulated colonic fluid			
7	64.81±2.33	67.17±0.33	60.11±1.34
8	72.79±1.17	73.11±0.12	67.09±1.51
9	79.22±1.35	81.18±0.45	74.83±0.24
10	85.27±1.45	86.81±1.05	81.21±0.31
11	91.39±1.11	93.92±2.34	91.62±0.13
12	97.86±1.45	98.05±1.23	98.11±0.34

This dissolution enhancement of G-1–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, 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–RS-3 dissolution, it was recognized that resistant starch provides a good dissolution profile, but it releases a maximum drug (102.87% for RS-3) only up to a 16th h. The combination of MALTRIN® and dextran formulations

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**
Simulated gastric fluid)			
1	4.81±0.34	2.11±1.23	3.86±0.23
2	9.18±0.23	8.61±0.22	7.87±0.25
Simulated intestinal fluid			
3	14.87±0.31	12.69±0.17	11.82±1.34
4	17.98±0.23	15.81±2.01	15.39±1.11
5	23.11±0.25	19.09±2.03	19.17±2.11
6	28.16±1.23	22.81±1.22	24.16±0.23
Stimulated colonic fluid			
7	43.16±1.22	37.11±1.23	36.89±1.04
8	50.13±0.34	42.19±2.33	43.19±0.43
9	58.43±0.24	49.17±1.22	50.13±1.34
10	60.19±1.23	57.91±1.32	56.17±2.11
11	67.71±1.15	63.17±1.18	63.11±2.34
12	74.05±0.32	70.13±2.15	70.57±2.17
14	81.19±0.17	76.11±0.23	76.13±2.18
16	87.19±0.31	84.91±1.21	85.88±0.45
20	94.18±0.11	90.15±1.03	93.15±1.32
24	105.81±0.18	102.94±0.45	98.12±0.33

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**
Simulated gastric fluid			
1	7.18±0.23	07.71±0.23	06.18±1.05
2	15.94±1.34	16.66±1.34	11.90±0.32
Simulated intestinal fluid			
3	32.17±0.45	33.81±1.45	35.11±1.84
4	40.18±1.23	42.13±1.32	39.18±0.34
5	48.91±1.09	48.18±0.34	45.11±1.34
6	56.28±1.34	59.02±1.32	58.18±1.25
Simulated colonic fluid			
7	73.19±0.34	70.16±1.42	72.68±1.22
8	75.10±0.45	75.10±1.11	77.88±0.34
9	80.17±1.34	79.91±1.05	81.45±1.38
10	85.78±1.45	84.11±1.23	84.82±1.38
11	90.99±0.23	87.91±1.32	89.18±1.11
12	94.18±1.11	93.95±1.50	93.81±0.45
14	98.17±1.32	97.19±1.23	97.88±1.34
16	108.16±1.34	106.89±0.52	102.87±1.45

(D-1–D-3) was 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 produce dextranase enzymes, which cleaves dextran contents of the formulation (D-1–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 (Rt) and optimized D-3 was taken as a test sample (Tt). The similarity and difference factor were found to be 60.907 and 10.1651, which is within the specified limits [Figure 2]. At the 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

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

Time in hour	%CDR of Orthobid tablet (reference sample)-Rt	%CDR of test sample, D-3 -Tt	Rt-Tt	$(Rt-Tt)^2$	|Rt-Tt|
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 Rt=841.11	Difference factor (0-15) F1=10.1651	Summation of $(Rt-Tt)^2$=569.8778		Sum of |Rt-Tt|=85.5

Similarity factor (50–100); F2=60.9070

Table 10: Accelerated stability studies on D-3 formulation, as per ICH guideline Q1A (R2) at 40°C ± 2°C/75% RH ± 5% RH for 6 months

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±1.23	87.42±0.24	86.81±0.34	86.06±2.16	85.91±1.22	85.49±1.34
Friability (%)	0.670±0.14	0.762±0.04	0.826±0.05	0.862±0.04	0.890±0.34	0.956±0.31
Disintegration time (minutes)	5.16±0.23	5.34±0.04	5.28±0.23	5.32±0.34	4.29±0.34	4.08±0.53
Matrix integrity	Good	Good	Faire	Little moist	Partial erodible	Partial erodible

Table 11: As per ICH guideline Q1A (R2) *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±0.23	4.13±0.34	4.48±1.45	4.98±0.34	5.21±1.43	5.88±0.45
2	7.92±1.34	8.19±1.34	8.43±1.08	8.82±1.05	9.01±0.04	9.42±1.64
3	10.31±0.34	11.44±0.45	12.64±1.34	12.98±0.43	13.43±0.45	13.68±1.32
4	16.19±0.23	17.11±1.34	17.38±1.23	17.96±1.05	18.56±1.34	18.96±1.11
5	20.91±1.23	21.83±1.47	22.17±1.45	22.97±1.06	23.72±0.34	24.71±1.03
6	25.08±0.34	26.11±1.04	26.98±1.07	27.26±0.34	27.92±0.42	28.19±1.18
7	38.33±1.67	39.46±1.05	40.91±1.39	41.75±1.67	42.18±1.12	43.61±1.05
8	49.21±0.38	50.34±1.22	51.41±1.06	52.17±0.55	53.02±1.34	53.81±0.34
9	52.88±1.34	53.16±1.04	54.81±1.56	55.03±1.45	55.78±1.04	56.18±0.32
10	57.11±0.45	58.27±1.44	59.28±1.07	60.26±1.05	60.97±1.04	61.81±1.29
11	65.61±0.44	66.51±1.43	67.11±1.05	68.26±0.23	69.28±1.32	70.32±0.34
12	74.11±0.23	75.11±1.05	76.62±1.45	77.46±0.34	79.17±1.54	80.62±1.54
14	77.19±1.24	78.28±1.34	80.34±1.47	82.62±1.34	83.97±1.32	85.61±1.22
16	87.11±0.45	89.21±1.11	91.63±1.05	93.82±1.05	95.08±1.02	96.04±1.04
20	95.11±0.45	96.48±1.45	97.72±1.33	98.19±0.17	99.63±1.11	101.73±1.33
24	98.98±1.34	99.54±1.45	99.96±1.05	100.34±0.33	104.11±1.32	105.09±1.28

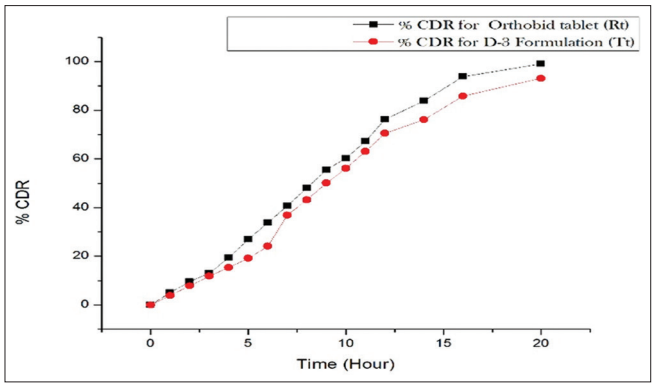

Figure 2: Percentage cumulative drug release of Ortho bed tablet and optimized D-3 formulation during similarity and dissimilarity study design

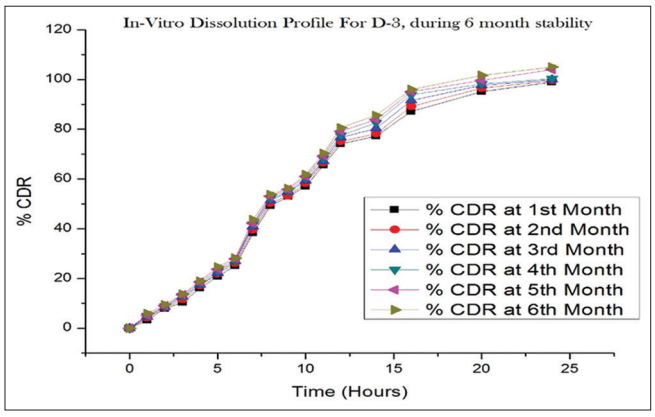

Figure 3: Dissolution profile of optimized D-3 formulation during 6 months accelerated stability studies

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

CONCLUSION

It had been a novel and challenging approach to preparing nanoparticle-based rofecoxib matrix tablets using a dry granulation technique. Since the formulation was specifically designed for colon targeting, hence various polysaccharides were used to formulate matrix tablets. 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 needs to be a warrant for a better understanding of dosage form behavior in bioavailability and dissolution profile.

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