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Formulation and Evaluation of Diclofenac Sodium Dual Type Mini Tablets for Extended Action

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ABSTRACT

In order to achieve rapid action and sustained release, we have fabricated dual type of mini-tablets of Diclofenac Sodium enclosed in a single capsule. 10 formulations of rapid release (IF1-10) mini tablets were prepared using sodium starch glycolate, Cross povidone and Micro crystalline cellulose. 12 formulations of sustained release (SF1-12) mini tablets were prepared by using HPMC, carbopol, Ethyl cellulose, xanthan gum and guar gum. All formulations were evaluated for pre-compression and post-compression parameters. Drug Excipient interaction was determined by FTIR, Short term stability studies were carried out at 40 ^{0}C /75 % RH for 3 months. Pre-formulation and studies conformed that all formulations showed better flow property. *In vitro* studies showed that all mini tablets in combination released more than 55 % within 30 min whereas marketed tablet Voveran SR 100 showed only 11 % release indicating the rapid drug release and the release was extended up to 80 % in 20th hour indicating the sustainability of the release. Natural polymers, Xanthan gum and guar gum containing formulations showed above 90 % in 12th hour indicating little rapid drug release when compared to synthetic polymers. FTIR report indicated no interaction of drug with excipients. Stability studies showed no significant loss in drug content, release profile and physical appearance. Hence it can be concluded that, the release profiles duel type mini tablets were quite promising for once a day formulation.

Keywords: Diclofenac Sodium, capsules, rapid release mini-tablets, sustained release mini-tablets.

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INTRODUCTION

Oral sustained release dosage forms are can be classified in to two categories one is single unit dosage forms (SUDFs), such as tablets or capsule and multiple unit dosages forms (MUDFs) such as granules, pellets and mini tablets[1]. The production of MUDFs is common strategy to release as different profile as compare to SUDFs.[2] MUDFs having different subunits of dosages form which is functionally equivalent SUDFs[3]. Mini-tablets usually characterized by diameter equal to or smaller than,2-3 mm [4] and these can be either filled into hard capsules or compacted into bigger tablets that, after disintegration, release these subunits as multiple dosage forms[5]. Fabrication of mini-tablets is easier and dose release can be maintained as per requirement. Having the different release profile so chances of dose dumping are less and minimizing the risks of high local drug concentration[6]. Diclofenac sodium is commonly used NSAIDs sold over-the counter (OTC) pharmaceuticals[7, 8]. It's preferable dose is 50 to 150 mg and in rapid release formulation 50 mg dose is consider as the loading dose[9]. As its half-life (2-3 hours) extended release of Diclofenac sodium is preferred in inflammatory condition such as ankylosing spondolitis, osteoarthritis, rheumatoid arthritis and they are contraindicated to asthma, urticaria, hypersensitive patient to Diclofenac sodium[10]. Filled capsules contains the mini-tablets of both rapid and sustained release the rapid release acts as loading dose while others acts as sustained for maintaining drug concentration throughout a day[9]. These project an attempt to fabricate dual type of mini-tablets with rapid and sustained release profile representing the loading and maintenance dose. Different Formulations were studied and they are optimized to achieve desired release profile. The manufacturing and evaluation procedure was standardized and stability of formulations evaluated after 3 months of storage at accelerated stability conditions as per different condition 40^0c/75%.

MATERIALS AND METHOD

Diclofenac sodium was obtained as gifted sample from vijayadep pharmaceutical, Nepal, sodium starch glycolate, crosspovidone, anhydrous dibasic calcium phosphate, microcrystalline cellulose, mannitol, HPMC 15 cps, ethyl cellulose, carbopol lactose, magnesium stearate, talc was taken from S.D. Fine Chemical, Mumbai Capsule was obtained from the gift sample from Natural Capsules limited, Bangalore.

Pre-formulation studies[11]

Angle of repose

Angle of repose is the maximum angle possible between the surface of a pile of the powder and the horizontal plane. It was measured by the fixed funnel and free standing cone methods.[13] Funnel is

secured with its tip at a given height, h, which was kept 2cm above graph paper that is placed on a flat horizontal surface. Angle of repose can be determined by following equation:

$$\theta = \tan^{-1}(\frac{h}{r})$$

Where, $\theta$is the angle of repose,

h is height of pile, r is radius of base of the pile.

Bulk Density (D_b)

Bulk densities were determined by taking a quantity of 2 gm of granules from each formula which was light shaken for break of agglomerates formed was introduced into the 10 ml measuring cylinder. The volume was noted as bulk volume. D_b can be calculated by following formula:

It is expressed in gm/ml and is given by

$$D_b = \frac{Mass\ of\ powder}{Bulk\ volume\ of\ thepowder}$$

Tapped density (D_t)

Tapped densities were determined by allowed to fall down of bulk volume on cylinder its own weight from the height of 2.5 cm at 2 seconds intervals. The tapping was continued until no further change in the volume was noted. D_t can be calculated by following formula:

It is expressed in gm/ml and is given by

$$D_t = \frac{Mass\ of\ powder}{Tapped\ volume\ of\ the\ powder}$$

Carr's index

It is expressed in % and given by:-

$$Carr'sindex(\%) = \frac{Tapped\ density - Bulk\ density}{Tapped\ density} \times 100$$

Hausner's Ratio

Hausner's ratio was measured by the ratio of tapped density to bulk density.

$$Hausner's\ ratio = \frac{Tapped\ density}{Bulk\ density}$$

Preparation of Diclofenac sodium mini tablets [12]

Preparation of Rapid Release mini-tablets (RRMT)

RRMT of Diclofenac Sodium was prepared by direct compression method by using different superdisintegrants such as SSG, Crospovidone, and MCC, Magnesium stearate as lubricant. Before going to direct compression all the ingredients were screened through sieve no.100,except lubricant all the ingredients were thoroughly blended for15 min. After sufficient mixing lubricant

was added and again mixed for additional 2-3 min and compressed into 150mg each tablet using tablet compression machine equipped with 3 mm flat round convex punches in a rotary tablet press (lab press, Cip Machineries Ltd. Ahmedabad).The formulations are shown on Table 1.

Table 1: Formulation of Rapid Release mini-tablets

S.No	Ingredients	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9	IF10
1	Diclofenac sodium	50	50	50	50	50	50	50	50	50	50
2	Sodium starch glycolate	60	30	-	30	20	-	-	15	15	30
3	Cross-povidone	-	-	30	30	20	-	60	15	30	15
4	Microcrystaline cellulose	-	30	30	-	20	60	-	30	15	15
5	Anhydrous dibasic calcium phosphate	21	21	21	21	21	21	21	21	21	21
6	Mannitol	15	15	15	15	15	15	15	15	15	15
7	Magnesium sterate	4	4	4	4	4	4	4	4	4	4
8	Total	150	150	150	150	150	150	150	150	150	150

All ingredients are in milligram.

Preparation of Sustained release mini-tablets (SRMT)

Sustained release mini tablets were prepared by wet granulation method. Diclofenac Sodium and excipients were blended for 10 min and mixed with binder solution, PVP K30 in ethanol to form wet mass and passed through sieve # 10 and the granules were dried in an hot air oven (kemi, DTC-072) at 50^0C for an one hour. The dried granules again sieved through sieve number 16 and granules were mixed with require quantity of talc and magnesium stearate.Further tabletswere punched using 3 mm flat round convex punches in a rotary tablet press (lab press, Cip Machineries Ltd. Ahmedabad). The formulations wereshown Table 2.

Table 2: Formulation of Sustained Release mini-tablets

S.N	Ingredients	SF1	SF2	SF3	SF4	SF5	SF6	SF7	SF8	SF9	SF10	SF11	SF12
1	Diclofenac sodium	50	50	50	50	50	50	50	50	50	50	50	50
2	HPMC 15 cps	90	60	60	-	30	-	-	30	-	30	-	
3	Ethyl cellulose	-	30	30	60	30	-	30	-	90	30	-	-
4	Carbopol	-	-	-	30	30	90	60	60	-	20	-	-
5	Guar gum	-	-	-	-	-	-	-	-	-	20	90	
6	Xanthan Gum	-	-	-	-	-	-	-	-	-	-	-	90
5	Lactose	6	6	6	6	6	6	6	6	6	6	6	6
6	Dibasic calcium phosphate	15	15	15	15	15	15	15	15	15	15	15	15
7	Mag. stearate	6	6	6	6	6	6	6	6	6	6	6	6
8	Talc	3	3	3	3	3	3	3	3	3	3	3	3
9	Total	170	170	170	170	170	170	170	170	170	170	170	170

All ingredients are in milligram.

Evaluation of mini-tablets[11]

Hardness test

The hardness of the tablet was measured by using Pfizer hardness tester it is expressed in kg, six tablets were randomly taken from each formulation and mean and standard deviation was taken.

Friability

Pre-weighed tablet was taken and were rotated at 25 rpm for 4 minutes in a Roche friabilator (Campbell Electronics, Mumbai, India) and final weight of tablets were taken after friabilator. The friability of the tablet can be calculated by the following formula.

$$\%\ Friability = \frac{Weight_{initial} - Weight_{final}}{Weight_{initial}} \times 100$$

Weight variation

It was conducted by weighed randomly 20 tablets and calculated the mean weight and also weighed randomly each tablets. The specification of weight variation is 10 %.

Size and Uniformity

It was measured by using digital meter.

Drug content uniformity

20 mini tablets were crushed and powdered the 100 mg equivalent drug was taken and dissolve in a phosphate buffer 6.8 and appropriate dilution was done and measured the absorbance at 276 nm.

In-vitro dissolution studies[13]

The *in-vitro* dissolution studies were performed using the USP-II (Paddle) dissolution apparatus (Lab India) at 50 rpm.Dissolution media phosphate buffer pH 6.8. Medium is maintained at 37±0.5^{0}C. A 5ml was withdrawn at specific time intervals and same volume of fresh medium was replaced. The withdrawn samples were diluted with pH 6.8, filtered and analyzed on UV (Spectrophotometer UV-1800, Shimadzu).Spectrophotometer at 276 nm using pH 6.8 as a blank. Percentage cumulative drug release was calculated. Time duration for rapid release up to 1 hour and for sustained and combination of both rapid and sustained release up to 24 hour were done.

Kinetics studies[14]

For the analysis of release and release rate kinetics of tablets, data obtained were fitted into Zero order, First order, Higuchi matrix, and korsmeyer-peppas. According to ‘r’ values the best model was selected. The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows:-

1. Zero- order Kinetic model – Cumulative % drug released versus Time.
2. First- order Kinetic model – Log cumulative % drug remaining versus Time.
3. Higuchi’s model- Cumulative percent drug released versus square root of time.

4. Korsmeyer equation / Peppa's model- Log cumulative percent drug released versus log time.

Stability studies[15]

Accelerated stability study was carried out (Labtop, Sky Lab Instruments & Engineering Pvt. Ltd) by keeping at in air tight container at 40^0C/75% RH for 3 months. *In-vitro* evaluation of mini-tablets was carried out in each moment.

RESULTS AND DISCUSSION

All the reading were taken in triplicate

Pre-formulation study for the mini-tablets

The prepared granules were introduced for the pre-formulation studies the angles of repose of the granules were found to be in good range which shown flow properties was excellent. The bulk and tapped density of powder was determined. Compressibility index i.e. carr's index of the granules were determined and found good flow of powders. Haunser's ratios of granules shown good flow. These were shown on the Table 3 and 4 respectively.

Pre-Compression Parameter

Table 3: Pre-Compression Parameter of rapidrelease

Formulation	Bulk Density mean±sd (gm/ml)	Tapped Density mean ±sd (gm/ml)	Carr's index mean±sd	Haunser's Ratio mean±sd	Angle of repose mean±sd (degree(^{O}))
IF1	0.566±0.011	0.631±0.008	10.29±0.74	1.11±0.010	23.5±0.470
IF2	0.545±0.012	0.626±0.016	13.42±0.25	1.15±0.003	21.7±0.490
IF3	0.547±0.018	0.623±0.010	12.14±1.78	1.13±0.020	25.7±0.500
IF4	0.538±0.006	0.639±0.005	15.78±1.70	1.18±0.020	22.2±1.020
IF5	0.555±0.004	0.622±0.011	10.86±1.37	1.12±0.010	24.7±0.390
IF6	0.531±0.010	0.603±0.011	11.87±1.90	1.13±0.020	22.1±0.150
IF7	0.539±0.003	0.620±0.006	13.99±0.91	1.16±0.010	23.1±0.150
IF8	0.559±0.001	0.629±0.003	11.08±0.68	1.12±0.010	26.9±0.820
IF9	0.578±0.006	0.639±0.006	9.59±1.51	1.10±0.010	18.7±0.450
IF10	0.573±0.006	0.622±0.011	7.78±0.94	1.08±0.010	20.0±0.230

Table 4: Pre-Compression Parameter of Sustained Release mini-tablets

Formulation	Bulk Density mean±sd	Tapped Density mean ±sd	Carr's index mean±sd	Haunser's Ratio mean±sd	Angle of repose mean±sd
SF1	0.567±0.007	0.640±0.010	12.06±0.79	1.13±0.010	21.4±0.310
SF2	0.596±0.007	0.650±0.008	8.83±0.26	1.09±0.003	19.8±0.300
SF3	0.570±0.009	0.630±0.010	8.61±0.89	1.09±0.010	17.9±0.200
SF4	0.570±0.008	0.650±0.010	12.19±0.43	1.13±0.005	18.3±0.140
SF5	0.570±0.008	0.650±0.008	12.05±0.97	1.13±0.010	19.8±0.620
SF6	0.560±0.007	0.640±0.005	12.6±0.81	1.14±0.010	20.6±0.540
SF7	0.570±0.007	0.640±0.008	10.51±0.43	1.11±0.005	21.7±0.730
SF8	0.540±0.001	0.620±0.003	13.92±0.59	1.16±0.007	25.3±0.900

SF9	0.570±0.010	0.650±0.008	12.79±0.99	1.14±0.010	22.3±1.050
SF10	0.550±0.003	0.650±0.008	15.45±0.63	1.18±0.008	21.9±0.450
SF11	0.546±0.003	0.635±0.004	13.87±0.41	1.16±0.005	22.2±0.770
SF12	0.560±0.003	0.658±0.003	14.88±0.92	1.17±0.010	19.2±0.300

Post-Compression Parameters

Table 5: Post-Compression Parameters of Rapid Release

Formulation	Weight variatin mean±sd (mg)	Hardness mean±sd (kg/cm^2)	Friability mean±sd (%)	Thickness mean±sd (mm)	Drug content mean±sd (%)
IF1	149.95±2.12	3.53±0.057	0.21±0.010	3.06±0.05	99.37±0.70
IF2	150.64±4.62	3.76±0.200	0.20±0.020	2.9±0.05	99.12±0.81
IF3	151.10±2.60	3.96±0.200	0.19±0.020	2.9±0.05	99.62±1.62
IF4	151.29±1.70	3.90±0.100	0.17±0.001	3.0±0.15	99.83±0.46
IF5	150.15±4.17	4.20±0.150	0.08±0.005	3.0±0.11	99.66±0.01
IF6	149.78±4.81	4.16±0.057	0.16±0.010	3.1±0.11	99.37±0.24
IF7	150.92±3.42	4.23±0.110	0.17±0.005	3.1±0.10	99.15±0.80
IF8	149.49±4.03	3.46±0.150	0.20±0.010	2.9±0.05	99.68±1.38
IF9	150.32±4.61	3.50±0.100	0.25±0.010	3.0±0.10	99.83±0.43
IF10	150.61±3.18	3.63±0.200	0.19±0.010	3.0±0.05	99.60±0.74

Table 6: Post-Compression Parameters of Sustained Release mini-tablets

Formulation	Weight variation	Hardness	Friability	Thickness	Drug content (%)
SF1	169.59±1.15	3.83±0.11	0.11±0.01	3.7±0.05	99.97±1.22
SF2	169.53±1.83	3.93±0.05	0.18±0.01	3.3±0.11	99.18±0.83
SF3	170.12±1.34	3.93±0.11	0.35±0.01	3.7±0.05	98.19±1.25
SF4	170.03±1.72	4.13±0.11	0.40±0.01	3.8±0.20	99.76±1.18
SF5	169.62±2.03	4.13±0.05	0.15±0.01	3.7±0.05	98.98±1.14
SF6	170.22±1.76	3.80±0.17	0.16±0.02	3.6±0.05	99.19±1.07
SF7	169.50±2.06	3.83±0.05	0.20±0.02	3.6±0.05	98.93±0.93
SF8	171.00±1.94	4.00±0.11	0.24±0.01	3.7±0.05	99.55±0.15
SF9	169.90±1.44	3.70±0.05	0.22±0.01	3.8±0.05	99.21±1.17
SF10	171.30±1.15	4.06±0.05	0.19±0.02	3.8±0.15	99.41±0.52
SF11	170.60±2.17	4.03±0.21	0.29±0.02	3.8±0.09	98.93±0.25
SF12	170.80±1.47	4.03±0.12	0.38±0.01	3.6±0.06	98.80±0.36

Evaluation of physical properties of mini-tablets

The formulated tablets were evaluated. The hardness of tablets was found be good mechanical strength. Friability was found in less than 1%. Drug content uniformity of tablets was found in acceptable limit as per IP.

***In-vitro* dissolution studies**

The release profile of drug were studied by dissolution test and according to the Table 7 & 8 the release profile of drug were shown a good result the rapid release mini tablets within 60 minutes it gives 100% dissolution and within a 5 minutes gives preferable release as an rapid release dosage

forms. And sustained mini tablets also having the release of good sustained and gave excellent result which were study in a 24 hours and sample were taken in a different interval of the time. In the rapid release formulation sodium starch glycolate, cross-povidone and microcrystalline cellulose were used as a disintegrates by the different formulation of these disintegrates either single or combination of these disintegrates the best release profile was found on disintegrating containing sodium starch glycolate and microcrystalline cellulose having formulation shown that less release profile. In the sustained release formulation HPMC 15cps, ethyl cellulose and carbopol were used as a polymer. From where, best release profile were shown by the combination of each polymer in equal proportion. Ethyl cellulose and combination with carbopol were released within a 12 hours was shown by the release profile of SF6 and SF9 on Table number 8. The release profile of SF5 was best as the marketed product also shown on Table 8.The sustained release mini tablets also compared with a marketed product voveran SR 100 and result was found on good range and the combination of tablets was a good for the release profile for both rapid and sustained release. The best three formulation from each RRMT and SRMT were selected and study for release profile of combination of rapid and sustained release of nine formulation were carried out for 24 hours which gives the good results for a day showed both rapid as well as sustained release behavior, which was shown on Table 9.Dissolution profiles on graphical representation were shown on Figure 1 to 3. FTIR of drug and polymers were used to study the compatibility. There is no change in original peak shown that no interaction between drug and polymers data was not shown.

Table 7: Dissolution Profile of Rapid release mini-tablets

Time in min	% of CDR									
	IF1	IF2	IF3	IF4	IF5	IF6	IF7	IF8	IF9	IF10
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
5	69.13±1.81	67.60±0.95	62.40±0.60	68.83±0.95	67.63±0.80	43.94±0.67	67.40±0.69	65.46±1.06	66.17±1.20	64.44±0.93
10	84.30±0.84	81.64±1.40	66.11±1.49	73.08±1.33	81.78±1.38	46.02±1.60	81.44±1.18	79.89±1.11	79.59±0.87	73.87±0.92
15	91.60±1.01	85.56±4.02	71.98±1.64	83.58±1.57	87.33±2.14	56.58±0.82	88.51±0.60	83.60±0.95	86.76±0.96	84.37±1.10
20	95.26±0.81	90.10±0.98	77.17±1.14	89.95±1.05	92.29±1.71	62.90±0.92	93.18±0.91	87.83±1.05	89.99±1.14	90.85±0.65
25	98.22±0.66	92.84±2.37	83.20±0.79	93.50±2.63	93.72±1.08	69.46±0.90	95.72±0.71	91.06±1.12	93.64±0.70	94.71±0.70
30	100.29±1.02	95.07±0.88	88.85±1.18	97.47±2.58	97.08±0.88	72.80±1.01	97.36±0.64	95.33±2.94	95.27±0.71	96.35±0.75
35	101.44±0.26	97.12±3.34	95.24±1.39	100.14±1.03	98.83±1.07	81.45±0.90	99.21±1.08	97.98±1.12	98.33±0.80	99.01±1.13
60	102.60±0.55	99.78±0.59	97.08±1.62	102.41±1.02	103.44±1.27	88.52±0.89	101.28±1.24	99.32±0.71	100.39±0.24	102.80±0.33

Table 8: Dissolution Profile of Sustained Release mini-tablets

Time in hour	% of CDR												
	SF1	**SF2**	**SF3**	**SF4**	**SF5**	**SF6**	**SF7**	**SF8**	**SF9**	**SF10**	**SF11**	**SF12**	**Marketed**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
0.5	12.91±0.90	17.84±0.88	15.63±1.26	17.16±1.42	15.46±2.29	17.50±1.13	15.46±1.01	14.78±1.45	15.80±1.66	12.06±1.78	14.61±0.65	12.06±1.05	10.83±0.63
1	15.53±1.40	23.21±1.45	17.59±0.91	20.65±0.85	19.96±0.31	20.32±0.48	25.40±1.05	16.90±1.59	19.12±1.21	15.87±1.53	20.64±0.53	19.10±0.82	16.75±1.41
1.5	20.72±2.84	28.26±1.06	22.10±3.19	22.13±2.45	24.32±1.46	21.79±0.88	29.11±0.46	21.41±1.20	22.11±0.08	20.37±2.32	24.49±0.60	22.43±0.65	21.69±1.41
2	23.04±3.79	31.31±0.97	25.11±1.94	25.65±1.39	29.56±1.32	25.65±0.97	42.19±1.65	24.08±2.86	25.29±0.86	25.58±0.95	30.75±0.88	26.46±0.76	25.63±1.17
2.5	24.69±2.61	37.26±1.67	26.44±1.26	28.00±0.36	34.14±1.35	29.01±0.24	47.69±1.26	29.14±0.98	28.49±0.52	29.80±0.80	36.01±0.45	30.52±0.62	31.51±0.88
3	27.89±1.39	41.37±1.34	28.45±0.70	30.19±0.29	37.21±0.38	32.91±1.14	54.75±1.55	31.17±0.04	36.29±1.92	36.25±2.38	40.29±0.78	37.82±1.37	32.32±1.18
3.5	29.57±0.82	44.65±2.88	31.50±0.60	32.56±1.77	43.19±1.65	39.89±1.73	62.52±1.58	34.23±1.05	42.44±1.20	42.40±1.04	43.73±1.29	44.48±1.95	35.04±0.80
4	32.62±0.63	46.59±1.35	36.59±2.60	34.78±2.32	48.86±1.81	46.73±1.84	65.75±0.48	37.13±1.55	48.28±1.08	47.39±2.87	50.77±2.56	51.35±0.74	40.97±1.26
4.5	36.70±0.69	58.06±3.37	38.32±0.75	37.51±1.07	55.08±1.02	50.21±1.08	69.67±0.56	40.56±3.36	51.60±2.29	52.06±0.20	53.25±4.55	55.54±2.79	41.44±0.87
5	39.11±1.00	66.36±1.10	39.55±0.48	40.26±1.06	58.94±0.93	54.22±0.75	72.94±0.65	44.69±3.40	54.25±0.55	55.57±1.37	60.00±2.31	59.41±0.69	43.70±0.94
6	42.21±0.87	67.57±0.77	43.84±1.82	47.79±1.36	66.40±0.88	61.14±1.13	78.60±0.88	50.87±2.17	66.44±0.73	64.71±0.75	68.48±0.52	63.47±0.60	51.97±2.19
8	46.17±0.99	74.56±1.35	46.79±1.06	49.57±1.71	67.77±0.76	62.49±1.48	83.27±1.80	53.70±3.58	78.69±0.79	78.65±2.24	81.42±1.45	77.91±1.58	54.80±0.89
12	49.31±0.68	89.57±0.74	48.74±0.55	52.89±1.21	70.51±0.50	65.20±0.82	98.83±1.66	58.40±0.80	87.44±1.34	91.82±0.82	99.02±0.99	93.12±1.52	67.84±1.54
16	54.84±1.78	98.89±1.56	53.75±2.16	55.38±1.06	73.61±1.31	69.97±1.01	99.53±0.35	66.19±2.12	96.41±0.87	94.01±0.88	99.72±2.30	98.72±1.09	75.46±0.54

20	59.38±1.33	99.76±1.39	59.99±0.48	61.29±0.08	80.28±0.53	73.91±1.39	100.06±0.74	72.83±3.73	97.27±1.55	97.07±2.23	99.92±1.33	99.07±0.24	80.71±1.80
24	63.60±0.52	100.46±0.64	66.59±0.53	64.50±1.14	85.81±2.08	77.19±2.67	100.08±0.15	76.45±2.48	98.80±0.95	98.60±0.25	100.28±0.69	99.77±0.10	83.05±0.24

Table 9: Dissolution Profile of Combination of RRMT and SRMT

Time in min	% of CDR								
	IFI+SF4	**IF1+SF5**	**IF1+SF7**	**IF2+SF4**	**IF2+SF5**	**IF2+SF7**	**IF7+SF4**	**IF7+SF5**	**IF7+SF7**
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
5	37.05±0.90	37.94±1.01	36.16±1.00	35.78±0.59	37.94±1.01	35.27±2.43	36.16±1.10	38.19±0.95	38.19±2.73
10	47.62±0.50	48.01±0.95	45.09±0.98	45.21±1.05	46.86±2.47	43.82±1.44	44.83±1.18	46.61±2.88	46.61±3.52
15	51.44±2.01	52.33±1.17	50.30±1.15	48.39±2.13	49.92±3.1	47.38±4.04	49.79±0.60	52.46±1.37	52.46±4.80
20	52.08±0.93	55.76±1.98	54.11±1.58	51.95±1.39	52.33±4.02	51.95±2.15	52.97±3.15	54.49±0.52	54.49±2.25
25	53.99±0.18	56.53±1.64	56.27±2.22	54.24±0.43	55.64±0.30	54.24±1.32	56.27±3.94	56.02±0.79	56.02±1.78
30	57.80±1.91	59.83±1.70	60.08±1.53	57.80±2.77	56.78±3.57	55.51±3.11	57.42±2.11	58.05±1.37	58.05±3.64
35	59.83±1.72	59.96±1.23	60.72±1.27	59.20±2.17	59.57±0.57	58.56±2.49	59.58±2.82	60.08±1.45	60.08±0.25
60	60.34±0.62	60.47±0.82	61.36±1.32	59.96±2.41	60.47±0.82	61.99±2.41	60.34±3.06	60.85±1.47	60.85±0.44
90	61.10±0.71	63.01±1.21	64.28±1.25	60.72±0.99	61.10±3.65	63.64±2.34	61.10±1.65	61.99±2.25	61.99±3.65
120	61.48±1.15	64.28±1.02	71.89±3.69	61.36±1.01	61.48±4.44	68.85±1.78	63.01±1.96	63.13±1.74	63.13±1.86
150	63.39±0.78	66.69±0.81	73.93±2.36	62.37±2.25	65.04±2.33	70.25±4.09	63.39±0.63	66.56±0.66	66.56±1.69
180	64.15±0.82	68.09±0.16	77.87±0.32	64.40±0.37	68.21±0.32	75.96±3.19	65.17±1.68	67.71±0.60	67.71±1.45
210	65.04±0.69	68.85±0.39	81.17±0.32	66.44±1.53	70.37±2.84	80.41±1.02	68.47±4.99	68.72±0.35	68.72±1.78
240	65.93±1.58	72.66±0.66	83.46±1.71	67.58±1.44	72.03±1.00	81.55±1.67	68.85±3.64	74.05±2.76	74.05±1.62
270	66.82±1.49	74.82±0.99	84.22±1.26	69.10±0.18	75.84±2.63	83.46±0.06	69.99±1.38	76.60±3.94	76.60±0.50
300	67.83±1.51	78.00±0.30	87.78±1.76	70.76±1.25	79.14±2.00	85.24±3.19	71.39±2.34	78.12±0.37	78.12±1.65
360	69.23±0.84	79.90±1.57	89.68±1.56	72.03±1.85	81.43±4.21	88.03±1.35	73.30±0.34	81.55±4.43	81.55±2.38
480	69.99±1.01	83.20±1.11	93.11±2.22	72.79±1.58	82.70±0.55	90.57±2.39	74.19±0.87	83.46±1.51	83.46±1.89
720	75.07±0.85	85.24±0.61	98.83±1.30	74.57±0.32	84.73±0.51	96.03±3.80	75.33±1.47	84.60±0.68	84.60±1.62
960	76.85±2.23	87.52±0.60	99.47±0.48	76.60±2.02	86.51±1.81	97.56±2.83	77.87±4.21	86.00±2.65	86.00±0.99
1200	78.51±1.65	88.52±1.07	99.85±0.64	78.89±1.28	89.30±2.43	99.47±0.20	80.41±3.92	90.44±4.41	90.44±3.14
1440	83.33±1.09	92.09±1.08	100.1±2.66	81.68±2.23	91.08±0.97	99.47±1.59	81.55±2.01	92.10±1.10	92.10±0.95

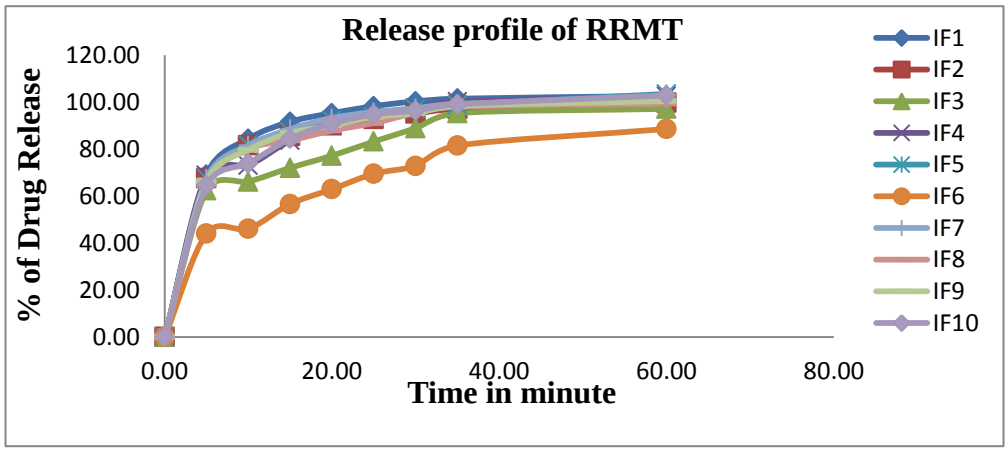

Figure 1: Release profile of rapid release mini-tablets

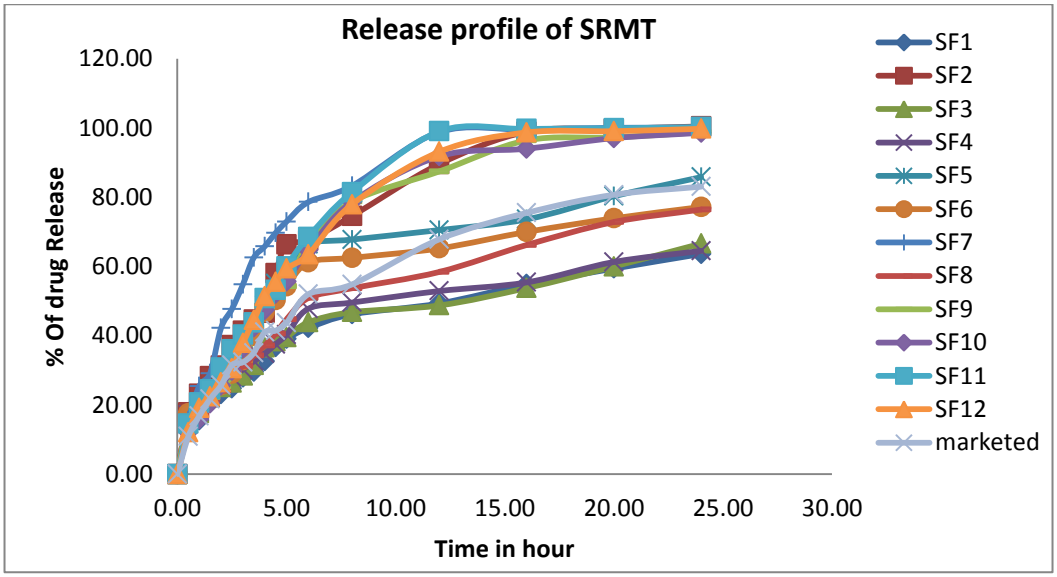

Figure 2: Release profile of sustained mini- tablets

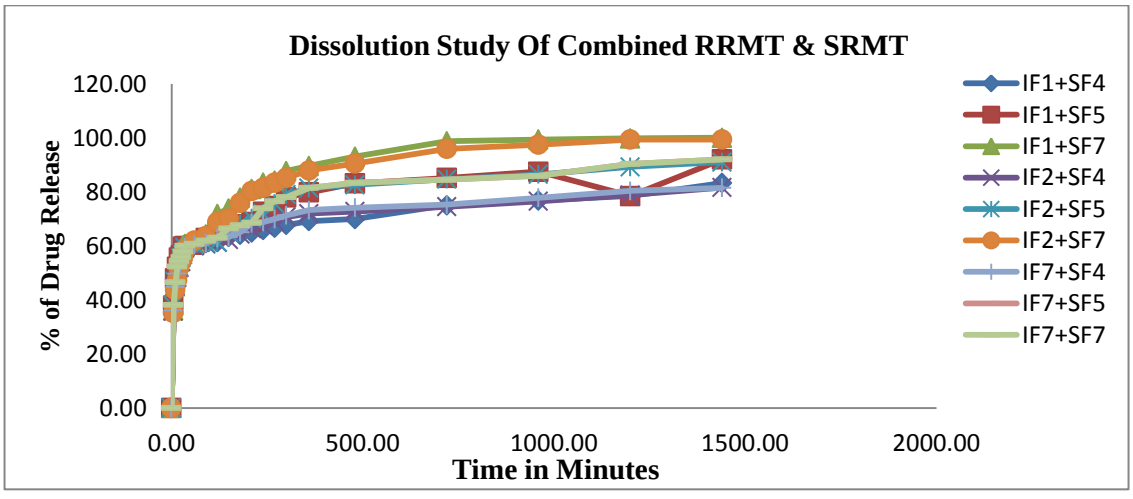

Figure 3: release profile of combination of RRMT and SRMT

Release Kinetics

Table 10: Release kinetic model of rapid release of RRMT

Formulation code	Kinetic models				
	Zero Order R^2	First order R^2	Higuchi R^2	Korsmeyer et al. N	R^2
RF1	0.431	0.748	0751	1.04	0.723
RF2	0.445	0.981	0.760	1.03	0.724
RF3	0.569	0.920	0.850	1.02	0.745
RF4	0.504	0.857	0.808	1.04	0.735
RF5	0.469	0.865	0.780	1.04	0.728
RF6	0.727	0.948	0.946	1.01	0.798
RF7	0.447	0.825	0.764	1.04	0.727
RF8	0.469	0.953	0.616	0.159	0.762
RF9	0.462	0.907	0.776	1.03	0.729
RF10	0.514	0.865	0.819	1.04	0.742

The examination of the correlation coefficient 'r' indicated that the drug release followed diffusion through first order mechanism which was shown on the Table 10. In rapid release the values for 'r' for first order (ranged from 0.9802 to 0.7482) found to be high in comparison to zero order (0.727 to 0.431) and Higuchi's square root of time (0.9462 to 0.6155). It was understood that rapid release to be first order pattern. Further, to understand the drug release mechanism, the data were fitted into peppas exponential model $M^t/M^\infty=Kt^n$, where M^t/M^∞ is the fraction of drug released after time 't' and 'K' is kinetic constant and 'n' is release exponent which characterizes the drug the drug transport mechanism. In rapid release values of 'n' is more than 0.89 shown that super II release. In other sustained release the value for 'r' for first order also (0.992 to0.8617) found to be high in comparison to zero order (0.861 to 0.678) and Higuchi's square root of time (0.983 to 0.724). So these sustained release also found to be first order pattern. The 'n' values lies in between 0.813 to 0.560 indicating non-fickian release mechanism was shown on Table 11.

Table 11: Release kinetic model of sustained release mini-tablets

Formulation code	Kinetic models				
	Zero Order R^2	First order R^2	Higuchi R^2	Korsmeyer et al. N	R^2
SF1	0.810	0.908	0.965	0.633	0.529
SF2	0.812	0.921	0.956	0.722	0.537
SF3	0.803	0.907	0.965	0.560	0.483
SF4	0.777	0.881	0.947	0.585	0.460
SF5	0.727	0.898	0.727	0.688	0.522
SF6	0.724	0.862	0.724	0.6603	0.506
SF7	0.678	0.885	0.678	0.722	0.508

SF8	0.837	0.952	0.838	0.670	0.542
SF9	0.823	0.992	0.823	0.769	0.593
SF10	0.813	0.993	0.813	0.813	0.636
SF11	0.796	0.857	0.941	0.186	0.896
SF12	0.810	0.987	0.948	0.320	0.357
marketed	0.861	0.978	0.983	0.734	0.598

Stability studies

The promising Formulations were subjected to short term stability study storing the formulation at 40^0C/75% RH for 3 months. The formulations IF-1 from rapid and SF-5 from sustained release drug were selected. The data for stability studies revealed that no considerable differences in drug content and dissolution rate were observed.

CONCLUSION

Differentially release mini-tablets of Diclofenac sodium was developed and filled in to capsule. The loading dose was maintained by rapid release mini-tablets and which becomes sustained by the sustained mini- tablets. The sustained release formulation was compared with marketed product voveran was found very good release profile. By the study of dissolution, disintegration from above formulation the best formulation was found to be IF1 from rapid release and SF5 from sustained release.

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