



FORMULATION AND EVALUATION OF DICLOFENAC SODIUM SUSTAINED RELEASE TABLETS USING MELT GRANULATION TECHNIQUE

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ABSTRACT

Hydrophilic polymers alone are not quite efficient in controlling the release of highly water soluble drugs. Hydrophobic Polymer and pore forming agent have been extensively investigated for sustaining the release of drug. They provide several advantages include good stability at varying pH ranges and effectively retards the water soluble drug. In the present study it was a novel approach where the water soluble drug is first incorporated in polymer matrix by melt granulation technique and this matrix is subsequently granulated with pore forming agent. Here it was considered that the combination of hydrophobic polymer and Pore forming agent to prepare the matrix tablets will result in desired slow release profile. Diclofenac sodium is selected as a model drug as it is water soluble and having short half life of 1-2 hours. Sustained release matrix tablets were developed by using hydrophobic polymer like Cetyl alcohol and pore forming agent like Pharmagrade sugar. Tablets containing 100 mg of drug were formulated. Flow properties of granules were studied by determining bulk density, tapped density, Carr's index, Hausner ratio for all the formulations were obtained in satisfactory range. Drug content, Weight variation, Hardness, Percent Friability, and Thickness and are within acceptable limits of pharmacopoeial requirement. To know the drug release kinetics Zero order, First order, Higuchi plot, Korsmeyer Peppas's plot were constructed^{3, 10, 11}

Key words: sustained release, melt granulation, release kinetics

INTRODUCTION

Diclofenac Sodium is official in the Martindale Extra Pharmacopoeia. It is a nonsteroidal anti-inflammatory agent used for a variety of painful and inflammatory conditions. It has a short biological half life 1-2 hours and is administered in a dose of 150mg 2-3 times a day. Therefore this drug is an ideal candidate for develop in lease dosage form which could result in prolonged clinical efficacy reduced frequency of administration and less side effects. The simplest and least expensive way to control the release of drug is to disperse it within an inert polymer matrix. Because of their simplicity and cost effectiveness hydrophilic gel matrix tablets are widely used for sustained release dosage forms. These materials form a gel like structure around the tablet core which sustains the release process Hydrophilic polymers are most widely used for preparation of matrix tablets. But use of Hydrophilic polymers alone for controlling the release of water soluble drug is probably restricted due to rapid diffusion of water soluble drug. Hydrophobic waxes have been extensively investigated for sustained release of drug. This provides good stability at varying pH and effective retarding of water soluble drug. In forming a wax matrix system different processing methods like dry blending, wet granulation, melt granulation and extrusion, are used. In the present study water soluble drug is first incorporated in waxy material and sugar by **melt granulation technique** and this granules were shifted and compressed in to tablets. In this study cetyl alcohol is taken as hydrophobic Polymer and Pharmagrade sugar is taken as a Pore forming agent which will help in drug release from matrix system^{1,10,11}

MATERIALS AND METHODS

Diclofenac Sodium is a gift sample from Arti Drug Ltd (Mumbai) Cetyl alcohol, Pharmagrade sugar, Talc, Aerosil, and Magnesium Stereate was purchased from Loba Chemicals, Mumbai. All the other chemicals and solvents are of analytical grade^{14 15 16}.

Preparation Of Granules By Melt- Granulation Technique

Initially the water soluble drug and Parma sugar were taken in Porcelain dish on a heating mantle and heated at a temperature of 75°C, and this melted wax is added in to drug sugar dispersion with continuous stirring, Then the mixture is allowed to cool and solidified at room temperature. The solidified mass is pulverized in mortar and sieved through a # 18 screen¹¹.

Evaluation Of Granules

The flow properties of the prepared granules were evaluated by determining the bulk density, tapped density, compressibility index (Carr's index), angle of repose, Hausner ratio³.

Preparation Of Blend For Compression

The prepared granules now blended with other accurately weighed ingredients as shown in the table. The cohesive mass is then passed through mesh no #12. Based on the drug content granules were weighed³

Evaluation Of Tablets

Hardness

Five tablets from each batch were selected and hardness was measured using Electro lab Digital hardness tester to find the average tablet hardness or crushing strength³.

Friability (%F)

20 tablets from each batch were selected randomly and weighed. These pre weighted tablets were subjected to friability testing using Roche friabilator for 100 revolutions. The tablet to the combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm and dropping a tablet at height of 6 inches in each revolution. Tablets were removed, de-dusted and weighed again. Following formula was used to calculate the friability³.

$$\%F = 1 - (\text{loss in weight} / \text{initial weight}) \times 100$$

Weight variation

Weight variation was calculated as per method described in USP. 20 tablets were weighed individually and the average weight is calculated. The requirements are met if the weights of not more than 2 of tablets differ by more than the

percentage listed in Table 8 and no tablets differ in weight by more than double that percentage.

Weight variation allowed as USPXX- NF XV

Average weight of tablet (mg)	Percentage difference allowed
<130	10
130-324	7.5
>324	5

Tablet thickness

Variation in the tablet thickness may cause problems in counting and packaging in addition to weight variation beyond the permissible limits. Tablet thickness should be controlled within a $\pm 5\%$ of a standard value. Tablet thickness was measured by Vernier caliper³.

Content uniformity

Five tablets were selected randomly and powdered. A quantity of this powder corresponding to 10 mg of Diclofenac sodium was dissolved in 50 ml of 7.2 phosphate buffer stirred for 60 min and filtered. 1 ml of the filtrate was diluted to 50 ml with 7.2 phosphate buffer. Absorbance of this solution was measured at 228 nm using 7.2 phosphate buffer as blank and content of Diclofenac sodium was estimated.

In vitro drug release/dissolution studies

The tablet samples were subjected to in-vitro dissolution studies using USP Type II dissolution apparatus at $37 \pm 2^\circ\text{C}$ and 50 rpm speed. As per the official recommendation of USFDA, 900 ml of 7.4 Phosphate Buffer was used as dissolution medium. Aliquot equal to 10 ml was withdrawn at specific time intervals and, The dissolution media volume was complimented with fresh and equal volume of 7.4 Phosphate Buffer. The aliquots were filtered and scanned with appropriate dilution and amount of Diclofenac sodium released from the tablet samples was determined spectrophotometrically at a wavelength of 276 nm by comparing with the standard calibration curve.

RESULT AND DISCUSSION

In present work the release data of F01, F02 and F03 are not under U.S.P Limit for dissolution of Sustained Release Tab.

In the present work, the formulations F04 to F08 *In-vitro* release studies were carried out for all the formulations as per USP type II tablet dissolution tester employing rotating paddle at 100 rpm using 900 ml of phosphate buffer of pH 7.4 as dissolution medium. The results were evaluated for 10 hr. As per the results of dissolution study formulations F04, F05, F06, F07, and F08 showed 73.4, 74.2, 83.4, 83.4, and 83.4 % respectively. From the above trial batches F01, F02, and F03 were released more compared to reference drug release. Where F05 and F06 batches were released less

compared to reference drug release. F07 and F08 batches drug released were nearest to the reference drug release. Above released data of F007 batch was match with reference so we can judge the optimized batch as F007.

The coefficient of determination (R^2) was considered as main parameter for interpreting the release kinetics. R^2 values for the zero order kinetics (0.909-0.952), first order kinetics (0.973-0.995) and Higuchi's kinetics (0.982-0.986). In order to predict the release mechanism, the data was subjected to Korsmayer-peppas treatment. The release exponent values were determined as shown in Table. F04, F05, F06, F07, and F08 formulations followed first order kinetic All batches followed Higuchi's plot since the regression coefficient (R^2) is found to be linear, this confirms that the drug release through the matrix was diffusion. Slope (n) value of F004, F04 and F05 formulations were between 0.5 to 1.0 so followed non- Fickian diffusion mechanism. Any formulation does not have (n) value greater than 1.0 so that case-II transport mechanism is not followed.

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Table 1: Formulation of Sustained release Tablets

Batch No		F01	F02	F03	F04	F05	F06	F07	F08
SR No.	Ingredient.	Qty/tab in (m.g)	Qty/tab in (m.g)	Qty/tab in (m.g)	Qty/tab in (m.g)	Qty/tab in (m.g)	Qty/tab in (m.g)	Qty/tab in (m.g)	Qty/tab in (m.g)
1.	Drug X	100	100	100	100	100	100	100	100
2.	Pharmagrade sugar	120	115	110	105	100	92	92	92
3.	Cetyl alcohol	15	20	25	30	35	50	50	50
4.	Povidone K90 Ph.Europe	7	7	7	7	7	7	7	7
5.	Aerosil 200 (Collodial Silicon Dioxide)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
5.	Purified Talc	3	3	3	3	3	3	3	3
7.	Magnesium stearate Ph.Europe (Veg origin)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
8.	Opadry Pink	1%	1%	1%	1%	1%	1%	1%	1%
	TotalWeight.	253 mg / tab	253 mg/tab	253 mg /tab	253 mg / tab	253 mg/tab	252 mg /tab	252 mg /tab	252 mg /tab

Table 2: Evaluation of granules blend of batches F01 to F08

BATCH	BULK DENSITY Gm/ml	TAPPED DENSITY Gm/ml	Hausner's Ratio	%COMPRESSIBILITY	ANGLE OF REPOSE	LOSS ON DRYING
F01	0.68	0.760	1.11	10.52%	28.20	1.53 %
F02	0.635	0.724	1.14	12.29 %	29.21	1.32 %
F03	0.640	0.770	1.25	16.88%	28.45	1.45 %
F04	0.621	0.732	1.17	15.16%	32.11	1.23%
F05	0.598	0.721	1.20	17.05%	24.10	1.10%
F06	0.651	0.722	1.10	9.8%	25.13	1.12%
F07	0.653	0.727	1.11	10.17%	24.17	1.13%
F08	0.654	0.723	1.10	9.54%	26.11	1.23%

Table 3: Compression Parameters

BATCH	WEIGHT (mg)	HARDNESS (kps)	THICKNESS (mm)	FRIABILITY (%)
F01	250 to 253	7 to 8	6.02	Less than 1 %
F02	250 to 253	7 to 8	6.01	Less than 1 %
F03	250 to 253	7 to 8	7.02	Less than 1 %
F05	250 to 253	8 to 9	7.04	Less than 1 %
F06	248 to 253	8 to 9	7.04	Less than 1 %
F07	248 to 252	8 to 9	7.03	Less than 1 %
F08	250 to 252	8 to 9	7.04	Less than 1 %

Table 4: In-vitro release of trial batches F01 to F08

Time (hrs)	% cumulative drug release							
	F01	F02	F03	F04	F05	F06	F07	F08
1	30	24.2	28	22.1	20.6	16.7	16.7	16.7
2	39	33.2	34	29.7	25.4	28	28	28
3	58	45.6	57	32.1	36.4	38.3	38.3	38.3
4	69.5	64.3	63	47.5	46.5	49	49	49
5	75	69.8	72	53.1	51.5	57	57	57
6	83	79.9	80.6	58.2	56.4	62.4	62.4	62.4
8	90.3	88.5	89	62.4	61.4	73.1	73.1	73.1
10	94.6	90.2	93	73.1	74.2	83.4	83.4	83.4

Table 5: U.S.P Limit For Extended Release Tab (Test 2)

Time in Hours	Amount Dissolve
1	NMT 28%
2	Between 20-40%
4	35-60%
6	50-80%
10	NLT 65 %

Table 6: Drug release profile of Reference Tablet

Time(hrs)	% Drug Release
1 HR	18.8
2HR	27.5
3HR	34.8
4HR	43.2
5HR	52.4
8HR	75.3
10HR	85.3

Table 7: First order release of trial batches F04 to F08 and Reference

Time (hrs.)	Log % cum drug retained					
	F04	F05	F06	F07	F08	Ref.
0	2	2	2	2	2	2
1	1.891537	1.899821	1.920645	1.920645	1.920645	1.909556
2	1.846955	1.872739	1.857332	1.857332	1.857332	1.860338
3	1.83187	1.803457	1.790285	1.790285	1.790285	1.814248
4	1.720159	1.728354	1.70757	1.70757	1.70757	1.754348
5	1.671173	1.685742	1.633468	1.633468	1.633468	1.677607
6	1.621176	1.639486	1.575188	1.575188	1.575188	1.562293
8	1.575188	1.586587	1.429752	1.429752	1.429752	1.392697
10	1.429752	1.41162	1.220108	1.220108	1.220108	1.167317

Table 8: Higuchi release of trial batches F04to F08 and Reference

Sq. Root of Time	% cumulative drug release					
	F04	F05	F06	F07	F08	Ref.
0	0	0	0	0	0	0
1	22.1	20.6	16.7	16.7	16.7	18.8
1.414214	29.7	25.4	28	28	28	27.5
1.732051	32.1	36.4	38.3	38.3	38.3	34.8
2	47.5	46.5	49	49	49	43.2
2.236068	53.1	51.5	57	57	57	52.4
2.44949	58.2	56.4	62.4	62.4	62.4	63.5
2.828427	62.4	61.4	73.1	73.1	73.1	75.3
3.162278	73.1	74.2	83.4	83.4	83.4	85.3

Table 9: Korsmeyer-Peppas release of trial batches F004 to F08 and References

Log Time	log % cum drug release					
	F04	F05	F06	F07	F08	Ref.
0	1.344392	1.313867	1.222716	1.222716	1.222716	1.274158
0.30103	1.472756	1.404834	1.447158	1.447158	1.447158	1.439333
0.477121	1.506505	1.561101	1.583199	1.583199	1.583199	1.541579
0.60206	1.676694	1.667453	1.690196	1.690196	1.690196	1.635484
0.69897	1.725095	1.711807	1.755875	1.755875	1.755875	1.719331
0.778151	1.764923	1.751279	1.795185	1.795185	1.795185	1.802774
0.90309	1.795185	1.788168	1.863917	1.863917	1.863917	1.876795
1	1.863917	1.870404	1.921166	1.921166	1.921166	1.930949

Table 10 : Mathematical models

Batch No	Zero order	First order	Higuchi	Peppas's Model	
	R ²	R ²	R ²	R ²	n
F04	0.909783	0.979823	0.982238	0.964377	0.542796
F05	0.92523	0.981153	0.986317	0.977087	0.580038
F06	0.952157	0.995039	0.982188	0.993855	0.70655
F07	0.952157	0.995039	0.982188	0.993855	0.70655
F08	0.952157	0.995039	0.982188	0.993855	0.70655
Ref.	0.974009	0.995039	0.968639	0.991045	0.682445

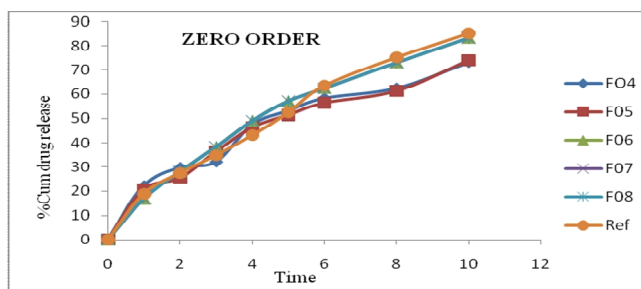


Fig 1 : Comparison of F04 to F08 With References Product With zero order release

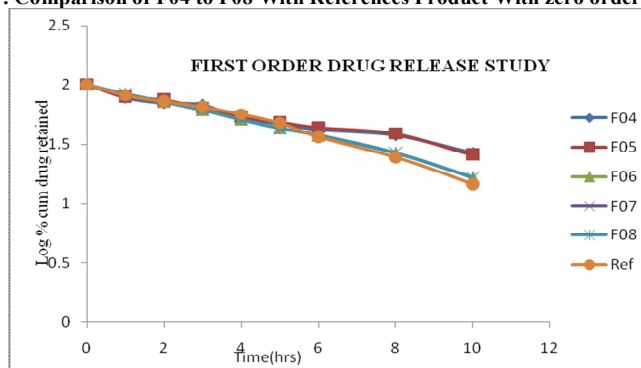


Fig 2: Comparison of F04 to F08 with References Product with First order release

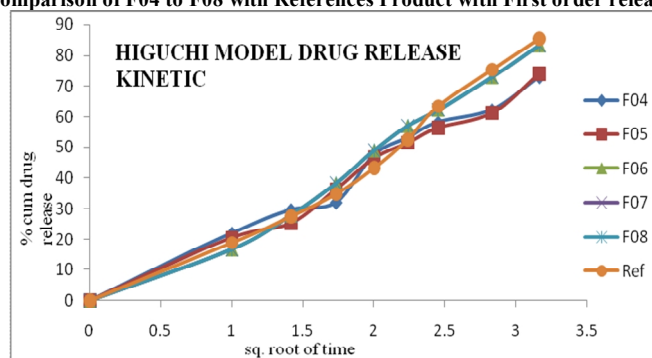


Fig 3: Comparison of F04 to F08 with References Product with Higuchi I Model Drug Release Kinetic

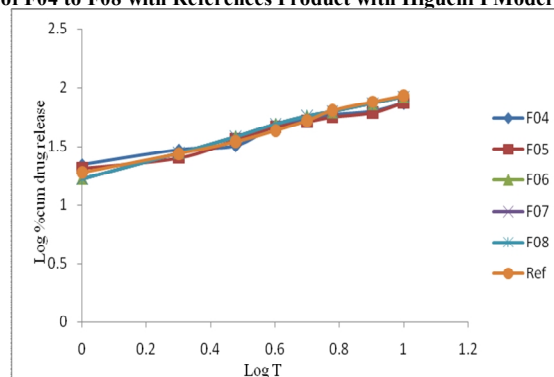


Fig 4: Comparison of F04 to F08 with References Product with Krosmeier -Pepaas Drug Release Kinetics.

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