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Formulation and *In-vitro* Evaluation of fast Disintegrating Tablets of Zaltoprofen

Sanjay K. Sharma*, Md. Nawaz Alam, Manish Jaimini, Arindam Chatterjee, Shailender Mohan

Department of Pharmaceutics, Jaipur College of Pharmacy, ISI-15, RIICO, Sitapura Institutional Area, Sitapura, Jaipur (Raj.), India.

Abstract

An attempt was made to formulate the fast disintegrating dosages form of Zaltoprofen using various superdisintegrants *viz.* sodium starch glycolate, croscarmellose sodium and crospovidone. FD tablets containing 80 mg of Zaltoprofen were developed with microcrystalline cellulose as binder and manitol as sweetener. The tablets were prepared by wet granulation method. The formulations were optimized on the basis of acceptable weight variation, friability, hardness properties and *in vitro* drug release. The results of dissolution studies suggested that formulations F9 exhibited maximum release. Applying the linear regression analysis and model fitting, the selected formulation F9 have showed diffusion (non-fickian) release mechanism, and shown to follow Higuchi release kinetics.

Keywords: Zaltoprofen, Fast Disintegrating Tablets, wet granulation method, *in-vitro* dissolution, release kinetic models.

Contents

Corresponding author
Sanjay K. Sharma
E-mail: sanjaysharma.pharma@gmail.com
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1. Introduction

A rapid-dissolving tablet (generally known as a fast-dissolving, fast-dissolving multi-particulate, mouth-dissolving, fast melting, or oro-dispersing tablets) is an oral tablet that does not require water for swallowing. The tablets get rapidly dissolved within 60 seconds when placed in the oral cavity. The active ingredients are absorbed through mucous membranes in the oral cavity and upper GI track and enter the blood stream. In general, the tablets are physically robust and can be packaged in multi-dose containers[1]. FDTs can be prepared by different methods as direct compression, freeze-drying, spray drying, sublimation and wet granulation method[2]. The aim of this study was to formulate FDTs with sufficient mechanical integrity and to achieve faster disintegration in the oral cavity without water.

To achieve this goal, microcrystalline cellulose was used as diluent and manitol as sweetening agent for the formulation of tablets. Attempts were made to enhance dissolution rate along with faster disintegration using superdisintegrants like croscarmellose sodium and sodium starch glycolate (SSG)[3] and crospovidone in the formulation of tablets. Zaltoprofen is a NSAID, with powerful anti-inflammatory and analgesic effects on inflammatory pain. Zaltoprofen is a preferential COX2 inhibitor, selectively inhibits PGE2 production at the site of inflammation. Zaltoprofen specifically blocks the nociceptive response induced by bradykinin. It has strong inhibitory effect on Bradykinin induced swelling and pain. The therapeutics use of Zaltoprofen includes lumbago, limited shoulder movement, rheumatoid arthritis, upper respiratory tract infection, post operative pain.

2. Material and Method

Zaltoprofen was gifted by Intas Pharmaceuticals Ltd., Ahmadabad (Gujarat). Cross Carmelose Sodium, Sodium Starch Glycolate and Crospovidone was purchased from the provider. All the ingredient used were of analytical grade.

Drug Identification Study:

The active pharmaceutical ingredient was identified by FTIR analysis of the sample obtained from sources. The sampling technique was mixing the API with the KBr and forming of the pellet which was then analyzed in 400-4000 wave number range by the FTIR Spectrophotometer.

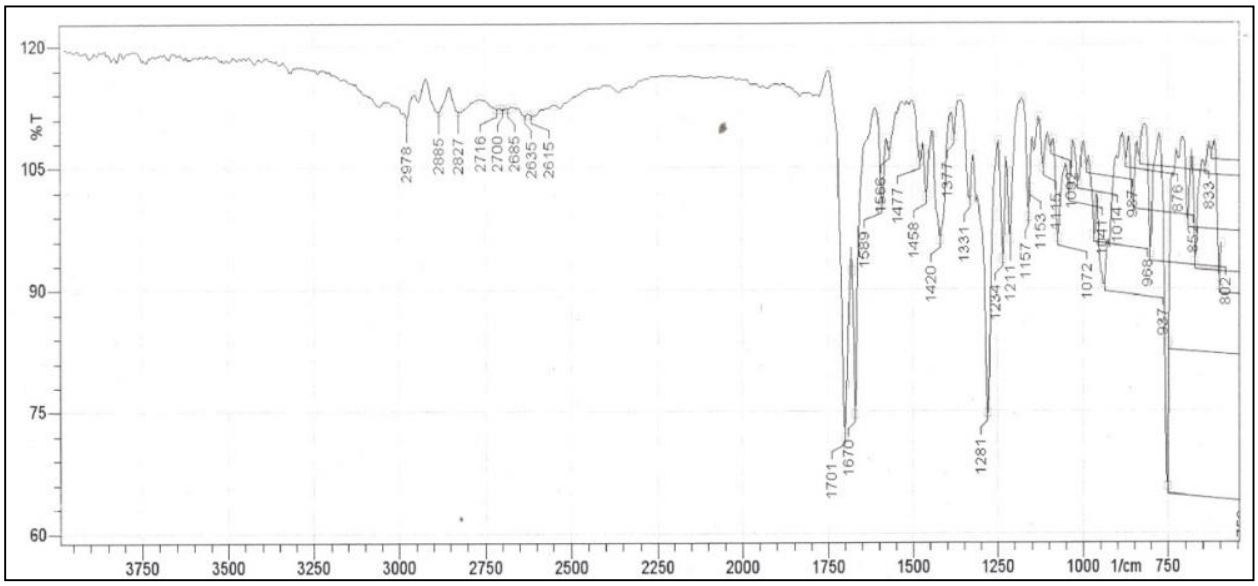

Figure 1. FTIR of Pure Zaltoprofen

Table 1. Composition of FDTs of Zaltoprofen

Formulation Code	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Zaltoprofen	80	80	80	80	80	80	80	80	80	80	80	80
Cross Carramelose Sodium	--	--	--	--	6	3	6	3	6	3	6	3
Crosspovidone	10	5	10	5	--	--	--	--	10	10	5	5
Sodium Starch Glycolate	10	10	5	5	10	10	5	5	--	--	--	--
Mannitol	20	20	20	20	20	20	20	20	20	20	20	20
Mag. Sterate	1	1	1	1	1	1	1	1	1	1	1	1
Micro Crystalline Cellulose	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Talc	1	1	1	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200	200	200	200

*All the ingredients were in mg

Preparation of Fast Disintegrating tablets:

The FDTs were prepared by mixing the ingredients in the proper proportion and then subjected to wet granulation. The following steps were followed during the preparation of the wet granulation layer:

Step-1:

Dry mix: Zaltoprofen, CCS, Crosspovidone and SSG were mixed in proper proportion according to the formula developed.

Step-2:

Granulation and drying of granules: The binder solution was added in dry mixed material in the mortar and the wet compact mass was passed through sieve and sifted wet granules were collected and kept for drying at a temperature of 100^0C for the reported period of time. The granules were dried in tray drier and sufficient drying was conferred by taking the LOD calculation into consideration, of the dried granules.

Step-3:

Lubrication:

After the drying of the granule, suitable lubricant (Mag. Sterate) was added to the granule so as to aid the flow property.

Step-4:

Compression: The granules were subjected to the compression using the suitable compression force.

Evaluation of the FD tablets of Zaltoprofen: The prepared tablets from each formulation batches were tested against the official standard evaluation parameters to ensure the proper manufacturing and release rate of the dosages of the drug.

Size, shape and thickness:

The size and shape of the tablets can be dimensionally described, monitored and controlled. The thickness of the tablets is the only dimensional variable related to the process of tabletting. At a constant compressive load, tablet thickness varies with the change in the die fill, with particle size distribution and packing of the particle mix being compressed, and with the tablets weight, while with the constant die fill, thickness varies with the variations in compressive load. The tablet thickness should be maintained well within a ± 5% variation of the standard value[4].

Weight variation:

20 tablets were selected at random and the average weight was calculated. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in the table [4, 5] and none deviates by more than twice that percentage[6].

Friability:

This test is applicable to compressed tablets and is intended to determine the physical strength of tablets and is measured by Roche Friabilator. For tablets with an average weight of 0.65 g or less take a sample of whole tablets corresponding to about 6.5 g and for tablets with an average weight of more than 0.65 g take a sample of 10 whole tablets. Dedust the tablets carefully and weigh accurately the required number of tablets. Place the tablets in the drum and rotate it 100 times. Remove the tablets, remove any loose dust from them and weigh them accurately. The test is run only once unless the results are difficult to interpret or if the weight loss is greater than the targeted value, in which case, the test is repeated twice and the mean of the three tests is determined. A maximum loss of weight (from a single test or from the mean of the three tests) not greater than 1.0 per cent is acceptable for most tablets. If obviously cracked, chipped or broken tablets are present in the sample after tumbling, the sample fails the test [6].

Hardness:

Hardness is the measure of the strength of the tablet to withstand the mechanical shock of manufacturing, packaging and transportation. Hardness is sometimes also referred to as tablet crushing strength. The hardness of the tablets is estimated by Pfizer hardness tester or Erweka tester [4].

Drug content:

10 tablets are taken randomly and weighed. The average weight is calculated and the tablets are then crushed in the mortar. The weight equivalent to the label claim is weighted accurately and is dissolved in 100 ml of the solvent (pH 6.8 phosphate buffer) being used for the dissolution study. The solution thus prepared is analyzed spectro-photometrically and the concentration is determined.

***In-vitro* dissolution study:**

This test is designed to determine compliance with the dissolution requirements for solid dosage forms administered orally. In vitro dissolution studies of FD tablets were studied using USP XXIII tablet dissolution test apparatus-I employing a paddle stirrer. 900 ml of pH 6.8 phosphate buffer was used as a dissolution medium. The temperature of the dissolution medium is maintained to 37 ± 0.5ºC. One tablet from each batch was used in each test. 5 ml of the sample of dissolution medium was withdrawn by means of pipette at known intervals of time and the sample was filtered using the whattman filter paper. The volume withdrawn at each interval was replaced with same quantity of fresh dissolution medium. The sample is analyzed, for drug release and release kinetics, spectrophotometericaly using UV-visible spectrophotometer (Shimadzu -1800) after suitable dilutions.

3. Result and Discussion

Drug Excipient Study: The drug excipient compatibility study was done by analyzing the sample of drugs with respective polymers by FTIR Spectrophotometer.

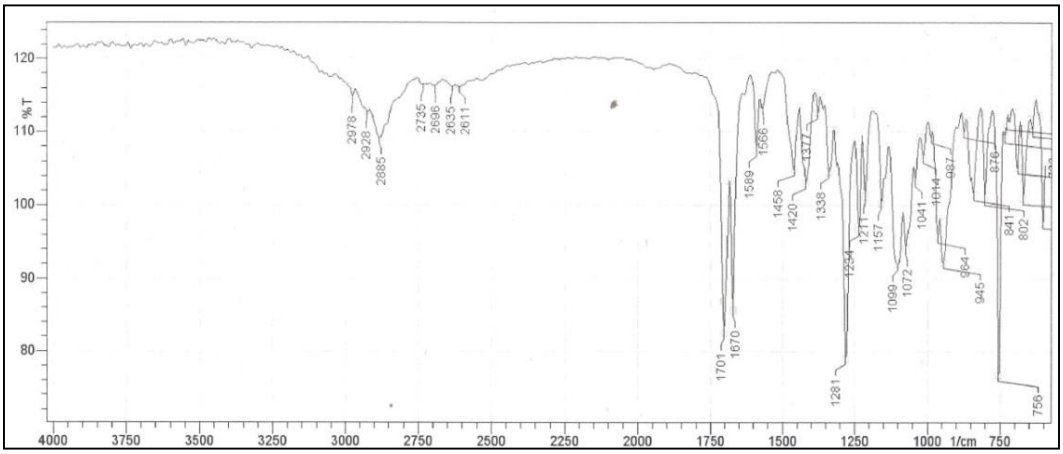

Figure 2. FTIR of Pure Zaltoprofen and CCS

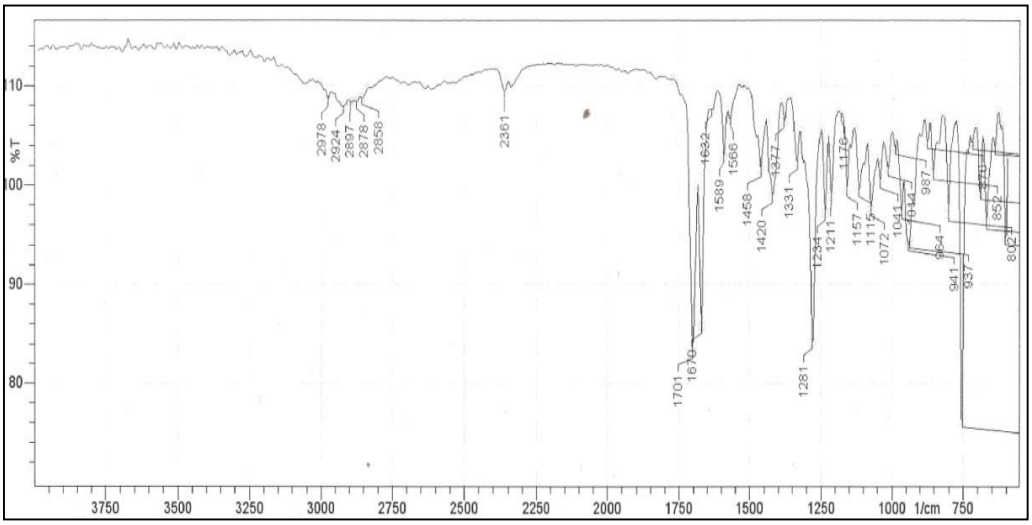

Figure 3. FTIR of Pure Zaltoprofen and SSG

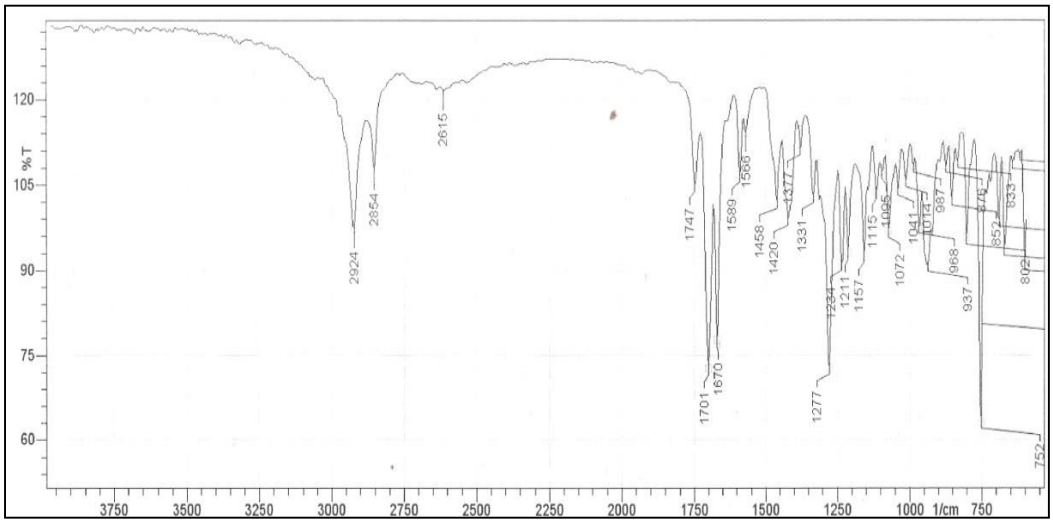

Figure 4. FTIR of Pure Zaltoprofen and MCC

Evaluation of Powder Blend of the best Formulations:

The powder blends of formulation batches were evaluated for the bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio.

Table 2. Physical Evaluation of granules of Formulation F1-F12

Formulation Code	Angle of Repose	Bulk Density	Tapped Density	Carr's Index	Hausner's ratio
F1	23.82±0.117	0.64±0.005	0.722±0.007	11.35±0.01	1.12±0.001
F2	24.45±0.220	0.65±0.005	0.734±0.007	11.44±0.01	1.12±0.005
F3	29.45±0.476	0.64±0.001	0.734±0.001	12.80±0.22	1.14±0.005
F4	21.67±0.502	0.65±0.001	0.732±0.005	11.20±0.07	1.12±0.005
F5	27.30±0.561	0.65±0.001	0.725±0.001	10.34±0.05	1.11±0.001
F6	24.29±0.206	0.64±0.001	0.734±0.007	12.80±0.07	1.14±0.002
F7	26.43±0.109	0.65±0.005	0.732±0.005	11.20±0.07	1.12±0.001
F8	21.82±0.117	0.64±0.005	0.722±0.007	11.35±0.01	1.12±0.001
F9	24.45±0.220	0.65±0.005	0.734±0.007	11.44±0.01	1.12±0.005
F10	27.45±0.476	0.64±0.001	0.734±0.001	12.80±0.22	1.14±0.005
F11	23.67±0.502	0.65±0.001	0.732±0.005	11.20±0.07	1.12±0.005
F12	22.82±0.117	0.64±0.005	0.722±0.007	11.35±0.01	1.12±0.001

The results of pre-compression parameters showed that all the powder blends have good flow property and compressibility which are essential for the preparation of the tablets from the powder blend.

Evaluation of FD tablets of Zaltoprofen:

Table 3. Physical properties of formulations F1 to F12

Formulation code	Thickness	Hardness	Friability	Weight variation	Disintegrating Time
Formulation code	Thickness	Hardness	Friability	Weight variation	Disintegrating Time
F1	2.451±0.01	4.50±0.27	0.809±0.05	201.67±1.27	32±1.1547
F2	2.448±0.01	4.34±0.25	0.939±0.07	199.26±0.20	23±1.5275
F3	2.459±0.01	4.10±0.25	0.821±0.01	200.34±0.48	31±1.5275
F4	2.451±0.01	4.50±0.27	0.709±0.05	201.67±1.27	32±1.1547
F5	2.438±0.01	5.51±0.25	0.976±0.04	200.33±0.12	32±1.5275
F6	2.436±0.01	4.12±0.27	0.836±0.14	199.60±0.28	26±1.5275
F7	2.452±0.01	5.20±0.25	0.627±0.03	200.43±0.71	30±1.5275
F8	2.451±0.01	4.50±0.27	0.809±0.05	201.67±1.27	30±1.1547
F9	2.448±0.01	4.34±0.25	0.739±0.07	199.26±0.20	23±1.5275
F10	2.451±0.01	4.50±0.27	0.709±0.05	201.67±1.27	32±1.1547
F11	2.436±0.01	4.12±0.27	0.736±0.14	199.60±0.28	36±1.5275

Table 4. Drug content of formulations F1-F12

Formulation Code	Drug Content
F1	100.21±0.39
F2	99.83±0.42
F3	98.53±0.41
F4	99.40±0.45
F5	100.61±o.42
F6	99.32±0.37
F7	100.01±0.25
F8	98.56±0.87
F9	100.17±0.38
F10	99.40±0.55
F11	100.52±0.43
F12	99.16±0.44

All the developed tablets were evaluated for weight variation, friability, thickness and hardness and the results are given in table. The percent deviation from the average weight was found to be within the prescribed official limits. Hardness of FD tablets was found to be in the range of 4.10 to 4.70 Kg/cm^2 and the friability of all the developed bilayer tablets was found to be in the range of 0.627 to 0.976 %, fulfilling the official requirements (not more than 1%). Thickness of tablets was found to be in the range of 2.436 to 2.460 mm. the mean disintegration time varies from 23 sec to 50 sec.

Table 5. *In-vitro* release data for Formulation F1-F6

Time (mins.)	% Cumulative Drug Release					
	F1		F1		F1	
5	29.079 ± 0.12	5	29.079 ± 0.12	5	29.079 ± 0.12	5
10	37.508 ± 0.14	10	37.508 ± 0.14	10	37.508 ± 0.14	10
15	47.623 ± 0.19	15	47.623 ± 0.19	15	47.623 ± 0.19	15
20	59.844 ± 0.11	20	59.844 ± 0.11	20	59.844 ± 0.11	20
25	70.802 ± 0.21	25	70.802 ± 0.21	25	70.802 ± 0.21	25
30	77.966 ± 0.17	30	77.966 ± 0.17	30	77.966 ± 0.17	30
35	86.395 ± 0.11	35	86.395 ± 0.11	35	86.395 ± 0.11	35
40	93.981 ± 0.21	40	93.981 ± 0.21	40	93.981 ± 0.21	40
45	96.931 ± 0.22	45	96.931 ± 0.22	45	96.931 ± 0.22	45

Drug content estimation data for all the batches are given in table. It was found to be in the range of 96.53 to 99.61 % for Zaltoprofen with low values of standard deviation indicating uniform drug content in the tablets developed.

***In-vitro* Dissolution Study of Formulations F1-F12:**

All the formulations of FD tablets were subjected to *In-vitro* dissolution study and the data was generated and various release kinetic models were implicated.

Table 6. *In-vitro* release data for Formulation F7-F12

Time (mins.)	% Cumulative Drug Release					
	F7	F8	F9	F10	F11	F12
5	41.1090 ± 0.21	29.0793 ± 0.21	42.9190 ± 0.24	34.7940 ± 0.21	35.8690 ± 0.15	8.5174 ± 0.21
10	45.9450 ±0.24	41.1090 ± 0.22	54.0460 ± 0.21	44.5040 ± 0.24	55.4340 ± 0.21	22.9970 ± 0.11
15	51.5870 ± 0.14	45.9450 ± 0.12	64.3780 ± 0.12	55.8320 ± 0.11	73.3690 ± 0.27	29.3850± 0.13
20	60.4540 ± 0.14	51.5870 ± 0.36	71.5310 ± 0.19	63.1150 ± 0.18	75.8150 ± 0.21	37.9024 ± 0.17
25	66.9020 ± 0.15	60.4540 ± 0.33	78.6840 ± 0.22	72.8250 ± 0.16	80.7060± 0.15	48.9751± 0.13
30	73.3510 ± 0.20	66.9020 ± 0.24	85.0430 ± 0.15	81.7260 ± 0.21	83.1510 ± 0.18	61.3253 ± 0.21
35	78.1870 ± 0.24	73.3510 ± 0.25	91.4010 ± 0.16	84.9620 ± 0.31	88.0430 ± 0.13	74.1014 ± 0.23
40	84.6350 ± 0.21	78.1870 ± 0.15	94.5800 ± 0.18	89.8170 ±0.15	91.3040 ± 0.13	82.6188 ± 0.11
45	90.2780 ± 0.22	84.6350 ± 0.20	97.7590 ± 0.11	94.6720 ± 0.21	95.3800 ± 0.17	87.7293± 0.13

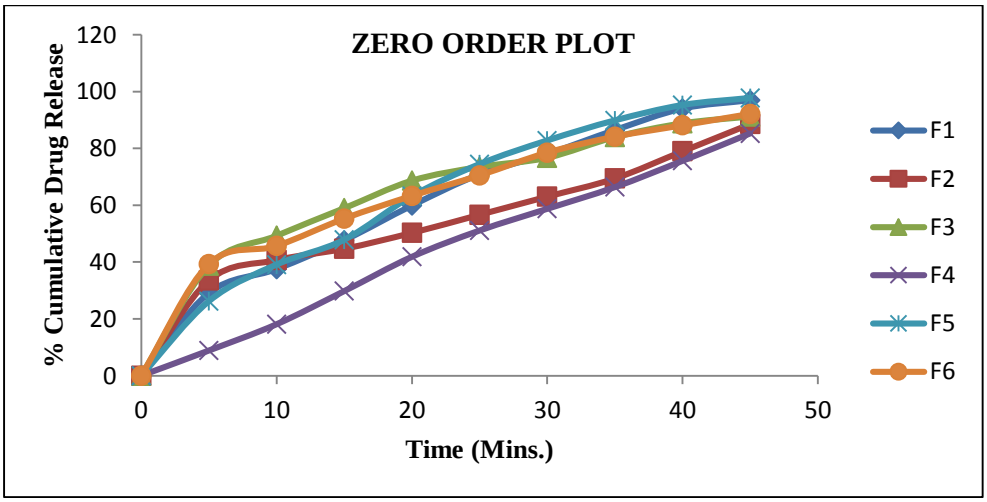

Figure 5. Zero order Plot for formulations F1-F6

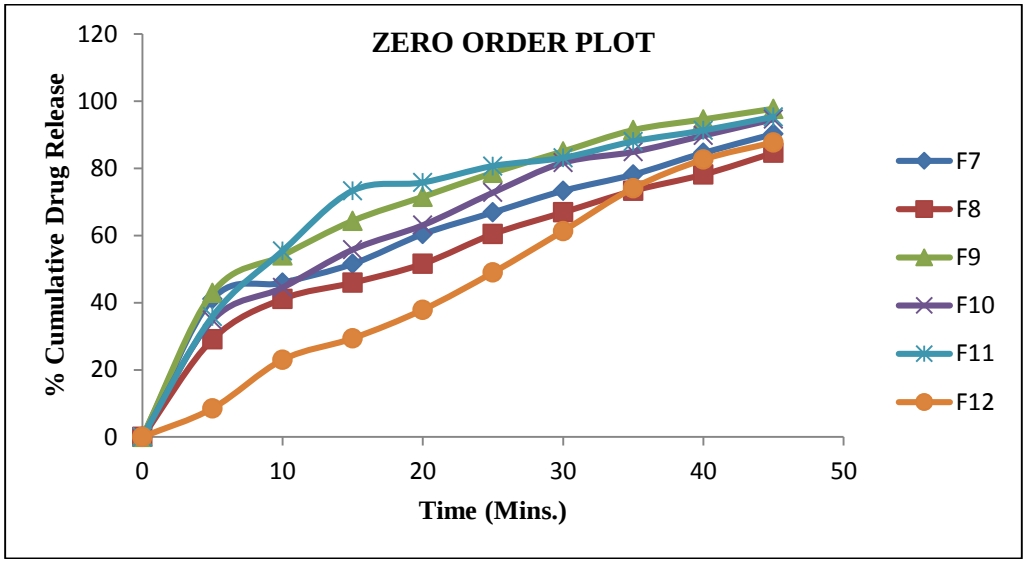

Figure 6. Zero order Plot for formulations F7-F12

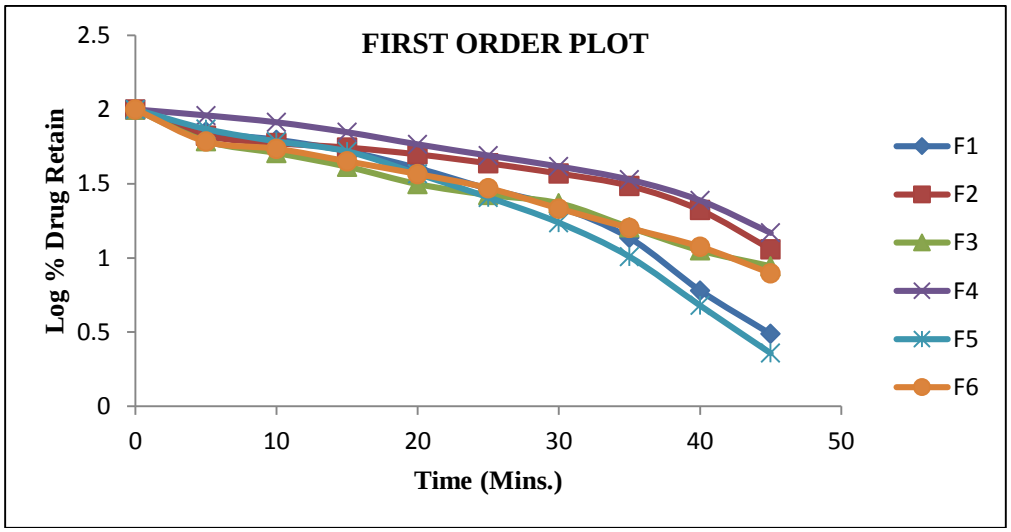

Figure 7. First Order Plot for formulations F1-F6

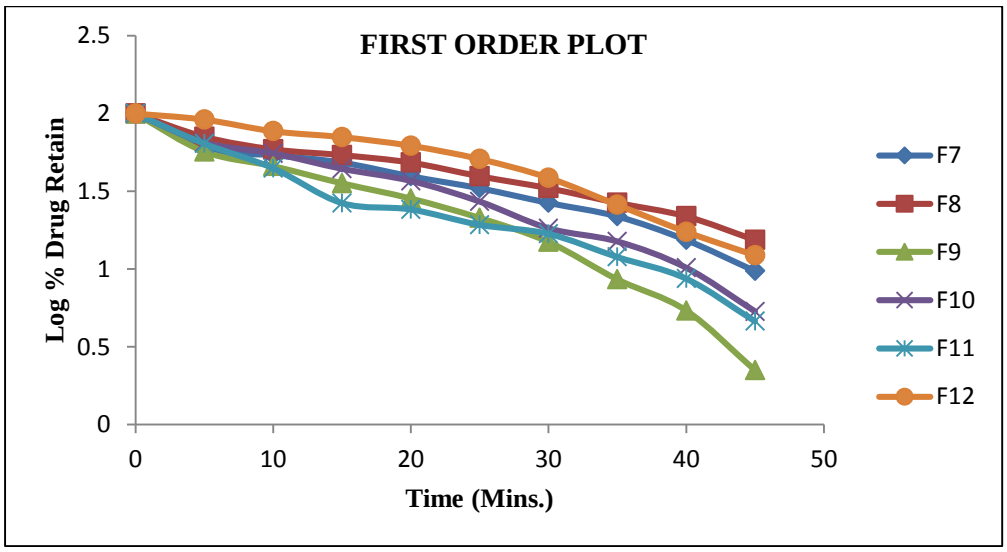

Figure 8. First Order Plot for formulations F7-F12

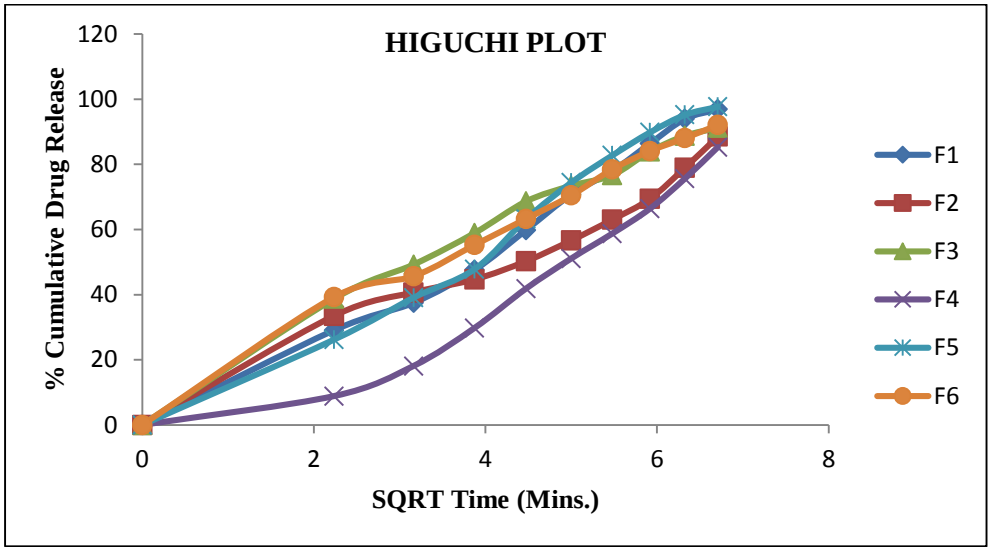

Figure 9. Higuchi Plot for formulations F1-F6

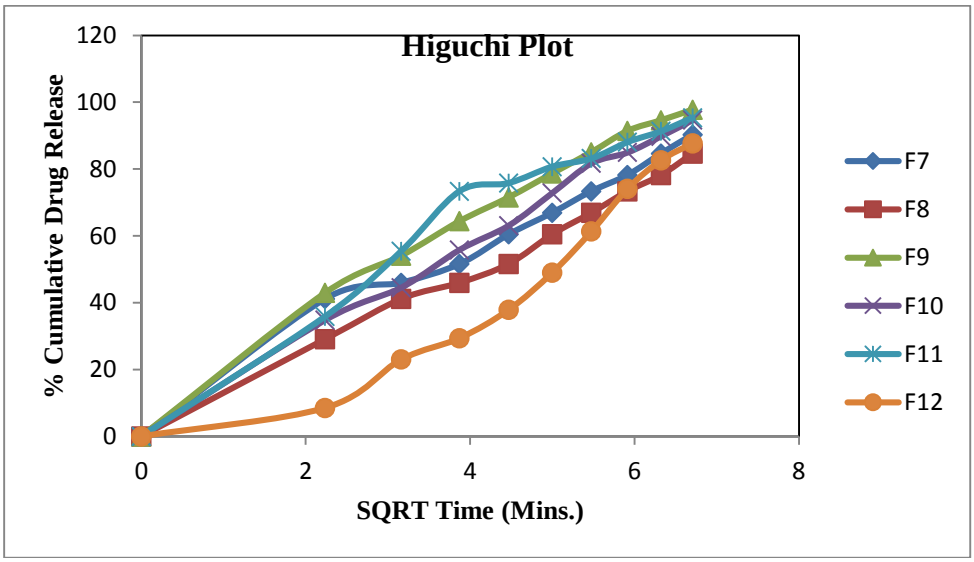

Figure 10. Higuchi Plot for formulations F7-F12

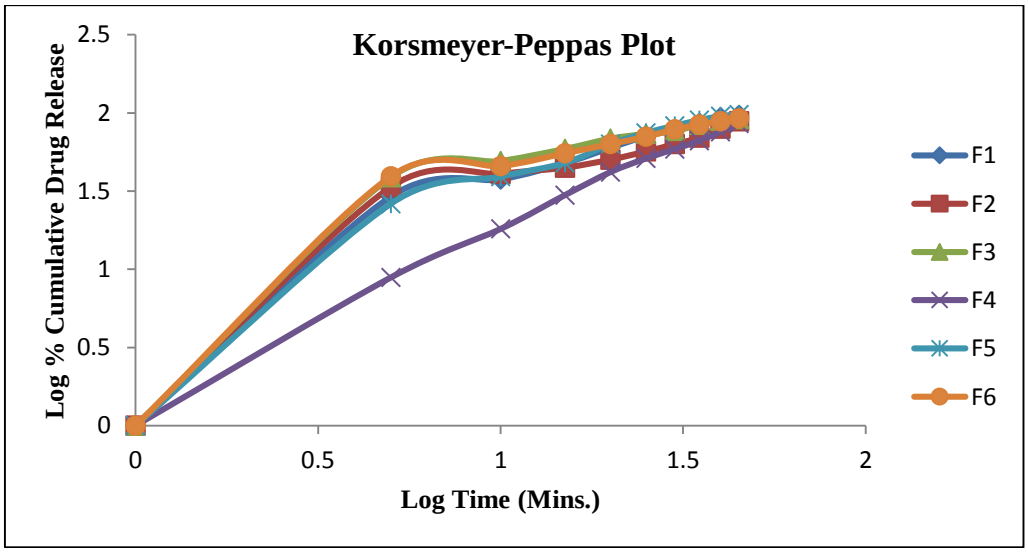

Figure 11. Korsmeyer-Peppas Plot for formulations F1-F6

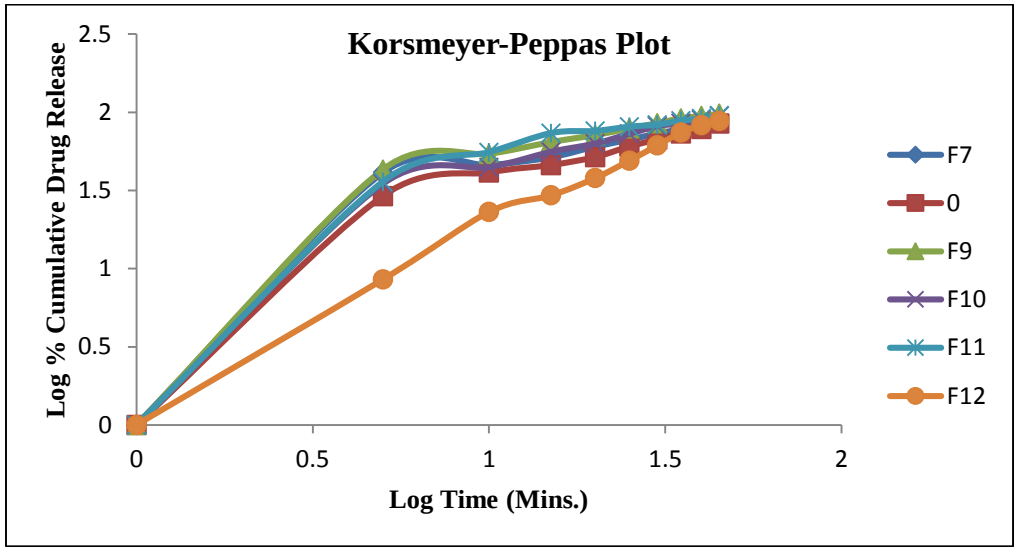

Figure 12. Korsmeyer-Peppas Plot for formulations F7-F12

The *in-vitro* data for the formulation is shown in tables and the graphs have been shown in figures. The formulation F9 shows the maximum release of about 97 %. It can be attributed to the lesser amount of MCC and higher concentration of superdisintegrants (CCS and crosspovide).

Table 7. Drug kinetic of FDT Formulation F9

Formulation Code	Zero order	First order	Higuchi model	Korsmeyer-peppas	Best Fit Model
	R^2	R^2	R^2	R^2	
F9	0.8474	0.9579	0.9872	0.830	Higuchi

For Zaltoprofen FDT formulations**,** the kinetic data of the best formulation F9 shown in table. The kinetics data of F9 formulation shown good fit in Higuchi Kinetic Release Model which indicated the best linearity.

4. Conclusion

An attempt was made to develop formulations for the fast disintegrating tablets of Zaltoprofen. In the present work, it was concluded that formulation F9 shows the best release that follows Higuchi release kinetics with anomalous diffusion method. Therefore, it can be concluded that the Zaltoprofen Fast Disintegrating Tablets can be prepared and have an advantages of patient compliance and improve the patient compliance by providing the better management of arthritis and pain.

5. Acknowledgement

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6. References

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