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Research Article

Formulation and Evaluation of Immediate Release Tablets of Zaltoprofen

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Abstract: Zaltoprofen is a nonsteroidal anti-inflammatory drug (NSAIDs) with powerful analgesic action on inflammatory pain. The purpose of this research work was to formulate an immediate release tablet of Zaltoprofen for the treatment of pain and inflammation, by using superdisintgrant such as Croscarmellose sodium and different grades of microcrystalline cellulose. Immediate release tablets of Zaltoprofen were prepared by direct compression method using superdisintgrant such as Croscarmellose sodium and different grades of microcrystalline cellulose in different ratios. Sodium starch glycolate was added to aid disintegration. Tablets were subjected to physicochemical characterization such as thickness, hardness, friability, weight uniformity, drug content, disintegration time, *in vitro* drug release, and stability study. Tablets were found to be satisfactory when evaluated for thickness, hardness, friability, weight uniformity, drug content, disintegration time and *in vitro* drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The *in vitro* drug release in optimized formulation F14 was found to be 98.89 % in 45 min. The optimized formulation F14 also showed satisfactory hardness (5.83±0.556 kg/cm^2), friability (0.425%±0.0029), drug content (98.29%±0.0657), weight variation (270.21±0.2184 mg), disintegration time (25.02±0.0028seconds) and stability.
Keywords: Pain and inflammation, Immediate release tablets, Superdisintegrants, NSAIDs.

INTRODUCTION

This research work is concerned with design and characterization of oral immediate release tablets of Zaltoprofen, in order to provide immediate relief from pain and inflammation. Immediate release drug delivery systems are designed to provide immediate drug levels in short period of time. Immediate release drug delivery is desirable for drugs having long biological half life, high bioavailability, lower clearance and lower elimination half life. But main criterion for immediate release dosage form is poor solubility of the drug and the need of immediate action of drug to treat unwanted defect or disease [1].

The tablet is the most widely used dosage form because of its convenience in terms of self-administration, compactness and ease in manufacturing. In pharmaceutical industries, manufacturers of generic tablets are usually focussed on the optimization of the excipient mixture to obtain a product that meets established standards [2, 3].

Zaltoprofen, 2-(10, 11– dihydro – 10 – oxodibenzo [b, f] thiepin – 2 - yl) pro-pionic acid is a potent nonsteroidal anti-inflammatory drug (NSAID) [4]. Zaltoprofen is a nonsteroidal anti-inflammatory drug (NSAIDs) with powerful analgesic action on inflammatory pain [5, 6]. It is a preferential cyclooxygenase (COX)-2 inhibitor [7].

NSAIDs are classified according to their chemical structure or their selective inhibition of COX-1 and COX-2. Zaltoprofen is a preferential COX-2 inhibitor [8] and selectively inhibits prostaglandin E2 (PGE2) production at inflammatory sites [9-13]. Zaltoprofen has a unique action in inhibiting bradykinin (BK)–induced nociceptive responses more potently than do other NSAIDs [5,14].

MATERIALS

Zaltoprofen was obtained as a gift sample from Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat, India. All other chemicals used were analytical grade and were used without purification. Double distilled water was used in the study.

METHOD

Immediate release tablets were prepared by the formula given in table 1. Direct compression method was employed using a combination of different grades of microcrystalline cellulose [15-25, 31, 33, 37]. Different grades of microcrystalline cellulose like Avicel pH 102 and Avicel pH 200 were sifted through sieve number 40 along with diluent directly compressible lactose. Sifted drug and disintegrants sodium starch glycolate and ac-di-sol were added and mixed thoroughly [26]. Sodium lauryl Sulphate was added to aid release. The prepared powder blend was

evaluated for various parameters like bulk density, tapped density, angle of repose, compressibility index and Hausner's ratio [27, 28]. This blend was then compressed using a rotary compression machine (Cadmach, Ahmedabad, India) using magnesium stearate as lubricant and colloidal silicon dioxide as glidant.

EVALUATION OF POWDER BLEND

Particle size distribution [29, 30]

The measurement of particle size distribution was performed by sieving method using vibration sieve apparatus. A sieve stack with six sieves in aperture progression was loaded with powder on to the coarsest sieve of the assembled stack and nest is subjected to mechanical vibration. After 10 min, the particles are considered to be retained on the sieve mesh; then weighed the powder retained in the sieves and the respective parameters were calculated.

Drug–Excipient Interaction Study [30-33]

The drug, polymer and other formulation ingredients were characterized by IR spectroscopy using a FTIR 8400S (Shimadzu, Japan). The spectra were taken by KBr discs method in the range of 4700–400 cm–1.

Bulk density [30-33]

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantity of powder was carefully poured in to graduated measuring cylinder through large funnel and volume was measured, which is called initial bulk volume. It is expressed in gm/ml and is given by the formula

$$\textbf{Bulk density} = M/Vo$$

Where, M = mass of the powder
Vo = bulk volume of the powder

Tapped density [30-33]

Ten gram of powder was introduced into a clean, dry 100 ml measuring cylinder. The cylinder was then tapped 100 times from a constant height and the tapped volume was read. It is expressed in gm/ml and is given by

$$\textbf{Tapped density} = M/Vt$$

Where, M = mass of the powder
Vt = final tapping volume of the powder

Angle of repose (θ) [30-33]

It is defined as the maximum angle possible between the surface of the pile of the powder and the horizontal plane. Fixed funnel method was used. A funnel was fixed with its tip at a given height 'h, above a flat horizontal surface to which a graph paper was placed. Powder was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The angle of repose was then calculated using following equation

$$\textbf{Angle of repose } \emptyset = \tan^{-1}(h/r)$$

Where, h=height of the pile
r=radius of the pile

Compressibilty index (Carr's index) [30-33]

Compressibility index is used as an important parameter to determine the flow behaviour of the powder. It is indirectly related to the relative flow property rate, cohesiveness and particle size. It is simple, fast and popular method for predicting flow characteristics. Carr's index can be represented by Equation

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

Hausner's ratio [30-33]

Hausner's ratio is used to predict the flowability of the powders. This method is similar to compressibility index. Hausner's ratio can be represented by Equation

$$\text{Hausner's Ratio} = \frac{\text{Tapped Density}}{\text{Bulk Density}}$$

EVALUATION OF TABLETS [34-36]

All the tablets were evaluated for different parameters as thickness, hardness, friability, uniformity of weight, disintegration time, drug content and *in vitro* dissolution study.

Dimensional Analysis

The thickness and diameter of tablets was determined using vernier caliper. Twenty tablets from each batch were used and average values were calculated.

Hardness

The Monsanto hardness tester was used to determine the tablet hardness. The tablet was held between affixed and moving jaw. Scale was adjusted to zero; load was gradually increased until the tablet fractured. The value of the load at that point gives a measure of the hardness of the tablet. It is expressed in kg/cm^2. For each formulation, the hardness of six tablets was determined and average value was calculated.

Weight variation

Randomly selected twenty tablets were weighed individually and together in a single pan balance. The average weight was noted and standard deviation calculated. The tablets pass the test if not more than two tablets fall outside the percentage limit and none of the tablet differs by more than double percentage limit. IP limit for weight variation in case of tablets weighting up to 120 mg is ± 10%, 120 mg to 300 mg is ± 7.5% and more than 300 mg is ± 5%.

$$\textbf{PD} = [(W_{avg} - W_{initial}) / (W_{avg})] \times 100$$

Where, PD = Percentage deviation,
W_{avg} = Average weight of tablet,
$W_{initial}$ = Individual weight of tablet.

Drug content

Tablets were crushed and the powder equivalent to 100mg of drug were accurately weighed and transferred to 50ml volumetric flask. To this flask, sufficient amount of distilled water was added to dissolve the tablets completely. Then, the volume of flask was made up to the mark with same solvent. From this solution, 1ml of the sample was pipetted out and transferred to 10 ml volumetric flask. The volume in the second flask was made up to the mark with distilled water. From this 0.6ml, 0.8ml, and 1ml samples were withdrawn and volume was made up to 10ml to maintain concentration within the beer's range. This final diluted solution was estimated UV spectrophotometrically at 340 nm.

Friability

Twenty tablets samples were weighed accurately and placed in friabilator (Roche friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear. The % friability was then calculated by

$$= [(W_{avg} - W_{initial}) / (W_{avg})] \times 100$$

Disintegration test

Disintegration is evaluated to ensure that the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. Disintegration test was carried out using tablet disintegration test apparatus (Electrolab, India) using distilled water without disk at room temperature (37±2°C).

***In-vitro* drug release**

In vitro dissolution studies for all the tablets were carried out using USP type II Dissolution apparatus (Electrolab, Mumbai, India). The dissolution medium used was 900 ml, mixture of phosphate buffer solution pH 6.8 and water (1:1) used as dissolution medium. The tablets containing 80 mg of zaltoprofen were weighed and then introduced into the dissolution medium. 1 ml aliquots were withdrawn at every 1 hour and replaced by 1 ml of fresh dissolution media (37ºC). The medium was stirred at 50 rpm using paddle at 37±0.5°C. The samples were collected, filtered through Whatman filter paper (0.45um) and analyzed after suitable dilution (if required) at 340 nm using UV-visible spectrophotometer against phosphate buffer (pH 6.8) as blank.

Stability studies

The stability studies were conducted by storing the optimized formulation tablets at 40 ± 2ºC/75 ± 5% RH in stability chamber for 45 days. The samples were withdrawn after 45 days and analyzed for various physical tests and drug release study.

RESULTS AND DISSCUSION

Immediate release tablet of Zaltoprofen were successfully prepared by direct compression method using superdisintgrant like croscarmellose soudium and varying the grades of microcrystalline cellulose, as per formulation table (Table no. 1).

Table 1: Formulations of Immediate Release Tablet of Zaltoprofen

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
Zaltoprofen	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80
Directly Compressible Lactose	160	100	100	100	80	-	-	-	-	-	-	-	-	-	-
Microcrystalline cellulose (Avicel pH 102)	-	-	60	30	40	-	160	80	100	97.3	94.6	60	60	60	60
Microcrystalline cellulose (Avicel pH 200)	-	60	-	30	40	160	-	80	60	60	60	100	97.3	94.6	91.9
Ac – di – sol (Crosscarmellose Sodium)	15	15	15	15	15	15	15	15	15	15	15	15	15	15	15
Sodium starch glycolate	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Colloidal silicon dioxide (Aerosil 200)	6	6	6	6	6	6	6	6	6	6	6	6	6	6	6
Magnesium Stearate	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
Sodium Lauryl Sulphate	-	-	-	-	-	-	-	-	-	2.7	5.4	-	2.7	5.4	8.1

Compatibility study

The FTIR spectral analysis showed that there was no change in any characteristic peaks of pure drug and excipients, which confirmed the absence of chemical interaction between drug and excipients. The FTIR spectra of pure drug and drug with excipients are given in Figure 1 and 2 respectively.

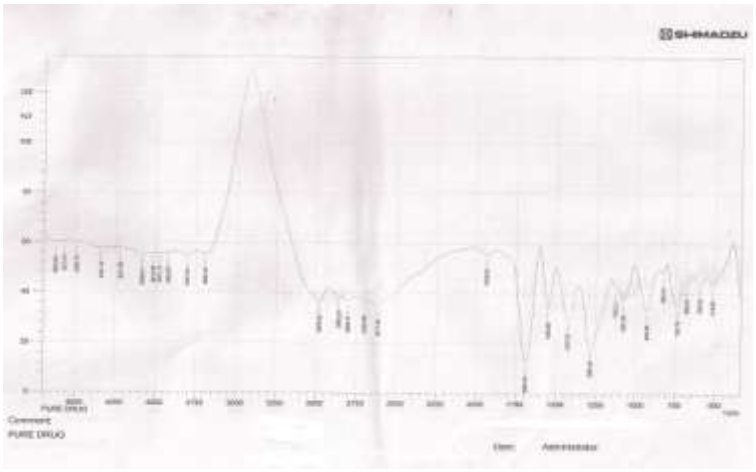

Fig. 1: FTIR spectra of Zaltoprofen

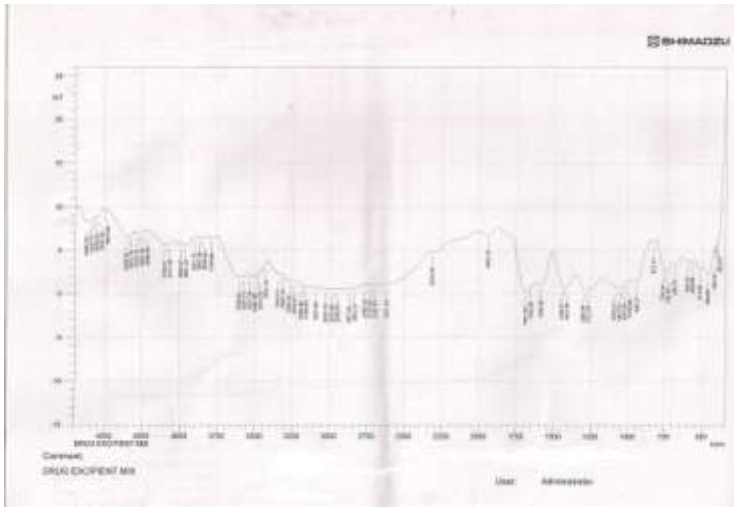

Fig. 2: FTIR spectra of Zaltoprofen with excipients

Mass -volume relationship

The characterizations of different formulation were done for determination of mass-volume relationship parameters. The evaluated parameters are bulk density, tapped density, compressibility index, and angle of repose, Carr's index shown in table 2.

Table 2: Evaluation of Pre compressed Powder Blend

Formulation Code	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose (θ)	Carr's Compressibility Index	Hausner's Ratio
F1	0.3525±0.0019	0.4840±0.0043	30.763±0.324	27.16±1.0438	1.3731±0.0196
F2	0.3279±0.0008	0.4709±0.0048	30.631±0.213	20.80±0.6574	1.2628±0.0105
F3	0.4355±0.0025	0.5782±0.0032	27.413±0.330	24.67±0.7104	1.3277±0.0125
F4	0.3661±0.0044	0.4805±0.0041	27.748±0.301	23.81±0.7456	1.3126±0.0128
F5	0.3852±0.0026	0.4991±0.0042	29.654±0.436	22.82±0.6827	1.2956±0.0114
F6	0.5039±0.0076	0.6380±0.0146	28.763±0.765	21.01±0.2798	1.2660±0.0045
F7	0.4923±0.0070	0.6052±0.0013	26.463±0.358	18.63±1.0889	1.2292±0.0165
F8	0.5104±0.0069	0.6152±0.0121	26.763±0.314	17.01±0.8365	1.2051±0.0122
F9	0.5159±0.0114	0.6772±0.0053	24.514±0.336	23.80±1.6335	1.3128±0.0284
F10	0.5116±0.0087	0.6207±0.0069	23.214±0.201	17.57±1.7219	1.2136±0.0251
F11	0.5040±0.0073	0.6068±0.0073	22.985±0.504	16.95±0.8713	1.2041±0.0126
F12	0.4897±0.0065	0.5892±0.0024	22.645±0.225	16.88±1.3210	1.2033±0.0189
F13	0.4874±0.0044	0.5686±0.0075	22.632±0.702	14.28±0.5358	1.1667±0.0072
F14	0.4849±0.0057	0.5694±0.0019	22.225±0.452	14.82±1.2643	1.1742±0.0017
F15	0.4940±0.0068	0.5856±0.0084	22.314±0.235	15.62±1.5644	1.1854±0.0217

All values are presented as Mean ±S.D.

Flow properties

The bulk density of the powder was in the range of 0.33-to 0.52gm/ml; the tapped density was in the range of 0.47 to 0.67gm/ml, which indicates that the powder was not bulky. The angle of repose of the formulations with lactose in larger quantity was in the range of 26º to 30º, which on increasing the quantity of microcrystalline cellulose decreased to the range of 22º to 24º which indicated good flow of the powder. The Carr's index was found to be in the range of 17 to 23 with the formulations containing lactose indicating poor compressibility of the tablet blend. This compressibility index decreased to the range of 14 to 16 on increasing the quantity of microcrystalline cellulose and eliminating lactose which improved the compressibility pattern.

Weight variation

The weight variation was prominent in the formulations with more lactose because of poor flow properties of the powder mixture. It ranged from 268 mg to 271 mg with very high values of standard deviation. On increasing microcrystalline cellulose the weight variation was significantly reduced. The results are shown in table no. 3. All formulations pass the weight variation test.

Table 3: Evaluation of Immediate Release Tablets of Zaltoprofen

Formulation Code	Hardness (kg/cm^2)	Friability (%)	Weight Variation (mg)	Content uniformity (%)	Thickness (cm)	Disintegration time (sec)
F1	5.31±0.1495	0.463±0.1900	271.43±3.0130	98.06±0.1002	4.88±0.0251	30.58 ±1.932
F2	5.53±0.2666	0.431±0.0056	268.97±1.8593	97.21±0.0003	4.21±0.0051	29.10± .0485
F3	5.40±0.1557	0.470±0.0127	270.36±1.3376	98.23±0.1020	4.62±0.0003	27.08±0.023
F4	6.00±0.1026	0.476±0.0085	270.15±0.7823	98.41±0.1142	4.56±0.0506	29.23±0.0569
F5	5.46±0.6784	0.521±0.0210	270.30±0.8602	99.03±0.0305	4.33±0.0761	27.00±0.0147
F6	5.44±0.5148	0.445±0.0061	270.39±1.3497	100.23±0.0142	4.81±0.0032	28.61±0.0025
F7	5.63±0.6513	0.504±0.0146	269.95±0.3993	98.54±0.0651	4.44±0.0062	26.21±0.0124
F8	6.01±0.1159	0.698±0.5421	270.90±0.4420	99.63±0.5241	4.58±0.0910	27.36±0.0005
F9	5.69±0.1400	0.679±0.3451	270.43±0.9639	98.61±0.2142	4.31±0.1001	25.09±0.0054
F10	6.07±0.0602	0.580±0.0053	270.59±0.2523	97.65±0.0806	4.25±0.0147	25.87±0.00
F11	6.03±0.0680	0.395±0.0315	270.88±0.3798	99.37±0.0547	4.61±0.0037	26.32±0.0052
F12	5.81±0.1692	0.401±0.0148	270.41±0.3255	98.72±0.0191	4.65±0.0154	27.43±0.0036
F13	6.17±0.5656	0.391±0.0159	270.93±0.2957	99.23±0.0140	4.70±0.0091	25.31±0.0001
F14	5.83±0.556	0.425±0.0029	270.21±0.2184	98.29±0.0657	4.62±0.0156	25.02±0.0028
F15	5.68±0.1184	0.437±0.0058	270.53±0.2332	97.88±0.0082	4.52±0.0213	25.64±0.0062

All values are presented as Mean ±S.D.

Tablet Thickness

Thickness of the formulations varied from 4.21±0.0051 to 4.88±0.0251mm.

Hardness

The hardness was uniformly maintained and it was found to be within 5.31±0.1495 to 6.17±0.5656 kg/cm^2.

Friability

The values of friability were within the limits except the formulations F8 and F9 where high friability was noted. These high values may be due to the change in the grade of microcrystalline cellulose.

Disintegration test

Tablets from each batch show immediate disintegration. Disintegration time varied between 25 to 30 seconds. This rapid disintegration is due to the rapid uptake of water from the medium, swelling and burst effect of Crosscarmellose sodium.

Percentage drug content

The percentage drug content of tablets of all batches was found to be 97.21 % to 100.23%, which was within the acceptable limits.

Drug release

Comparative cumulative percentage drug release data of all formulations are given in table no. 4. Dissolution profiles of formulations F1 to F8 and F9 to F15 are shown in Figure 3 and 4 respectively**.** Drug release for different batches was found to be 82.75 to 98.89 within 45 minute. The maximum drug release was observed in F14 among all formulations in 45 minute.

Table 4: Comparative % drug release profiles of formulation (F1-F15)

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
10	62.32	65.26	64.59	66.28	60.21	66.01	67.12	61.12	54.69	62.06	66.34	59.31	60.23	68.99	69.63
15	68.22	69.98	68.12	69.95	64.27	67.88	69.66	63.21	56.82	64.27	70.21	61.72	62.23	72.31	73.23
20	72.54	74.23	75.01	76.22	69.88	75.98	74.68	68.92	62.48	69.24	74.96	64.27	65.78	74.65	75.01
25	75.96	76.22	78.21	80.33	71.75	80.01	81.25	72.21	65.03	72.68	81.12	67.65	70.25	79.65	79.90
30	77.53	79.24	80.24	81.23	75.73	83.21	85.64	74.25	68.01	79.03	84.52	73.86	76.65	85.62	86.65
35	81.24	81.75	82.22	83.38	78.53	85.55	87.01	79.31	75.34	80.55	86.60	77.79	79.64	88.98	88.65
40	87.03	86.25	86.98	85.95	83.55	89.62	90.27	82.31	78.23	81.79	89.98	81.23	85.63	94.56	95.01
45	92.12	90.23	93.54	90.55	86.74	93.57	93.22	85.51	85.24	82.75	95.66	86.51	88.95	98.89	98.65

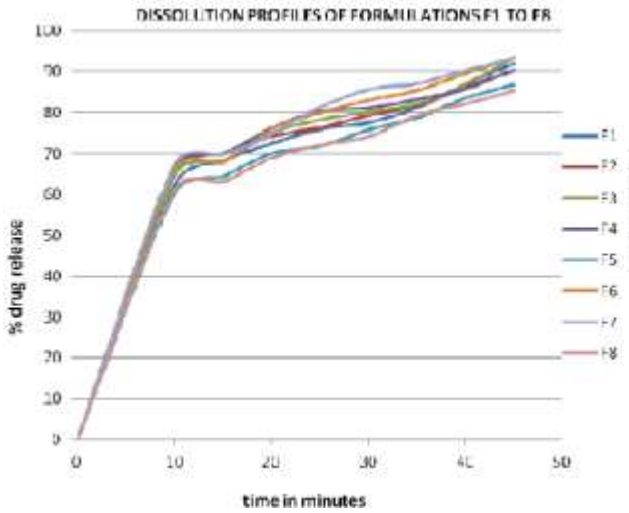

Fig. 3: Dissolution profiles of formulations F1 to F8

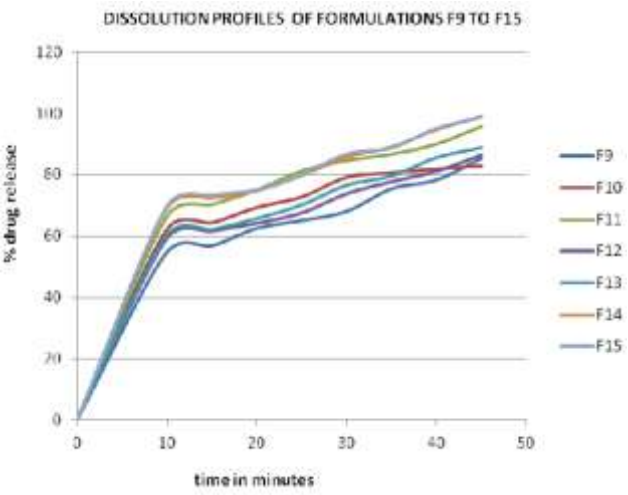

Fig. 4: Dissolution profiles of formulations F9 to F15

CONCLUSION

All formulations were found to be satisfactory when evaluated for thickness, weight uniformity, hardness, friability, drug content uniformity, disintegration time and *in-vitro* drug release. The tablet disintegration time was less than one minute for all the tablet formulations. The *in vitro* drug release in optimized formulation F14 was found to be 98.89 % in 45 min. The optimized formulation F14 also showed satisfactory hardness (5.83±0.556 kg/cm^2), friability (0.425%±0.0029), drug content (98.29%±0.0657), weight variation (270.21±0.2184 mg), disintegration time (25.02±0.0028seconds) and stability.

REFERENCES

1. Patel HP, Patel JK, Patel RR; Formulation Development & Optimization of Multiple Unit Particles System (mups) Containing Ramipril and Hydrochlorothiazide. International Journal of Pharmaceutical Sciences, 2010; 2(1): 448-456.
2. Gabrielsson J, Lindberg NO, and Lundstedt T; Multivariate Methods in Pharmaceutical Applications. J. Chemom., 2002; 16: 141-160.
3. Campisi B, Chicco D,Vojnovic D, Phan-Tan-luu R; Experimental Design for a Pharmaceutical Formulation: Optimization and Robustness. J.Pharm. Biomed. Anal., 1998; 18: 57-65.
4. Ito A, Mori Y; Effect of a Novel Anti-inflammatory Drug, 2-(10, 11-dihydro-10-oxo-dibenzo[b,f]- thiepin-2-yl)propionic acid (CN-100), on the Proteoglycan Biosynthesis in Articular Chondrocytes and Prostaglandin E2 Production in Synovial Fibroblasts. Res

Commun Chem Pathol Pharmacol., 1990; 70: 131-142.
5. Kameyama T, Nabeshima T, Yamada S, Sato M; Analgesic and Antiinflammatory Effects of 2-(10,11-dihydro-10-oxo-dibenzo [b,f]thiepin-2-yl)propionic acid in Rat and Mouse. Arzneimittelforschung., 1987; 37: 19–26.
6. Tsurumi K, Kyuki K, Niwa M, Kokuba S, Fujimura H; Pharmacological investigations of the New Antiinflammatory Agent 2-(10,11-dihydro-10-oxodibenzo[b,f] thiepin-2-yl) propionic acid.1st Communication: Inhibitory Effects of Rat Paw Edema. Arzneimittelforschung., 1986; 36: 1796–1800.
7. Hirate K, Uchida A, Ogawa Y, Arai T, Yoda K, Zaltoprofen A; Non-Steroidal Anti Inflammatory Drug, Inhibits Bradykinin-Induced Pain Responses Without Blocking Bradykinin Receptors. Neurosci Res., 2006; 54: 288-294.
8. Kawai S, Nishida S, Kato M, Furumaya Y, Okamoto R, Koshino T, Mizushima Y; Comparison of Cyclooxygenase-1 and -2 Inhibitory Activities of Various Nonsteroidal Anti-inflammatory Drugs using Human Platelets and Synovial Cells. Eur J Pharmacol., 1998; 347: 87–94.
9. Beiche F, Scheuerer S, Brune K, Geisslinger G, Goppelt-Struebe M; Up-Regulation of Cyclooxygenase-2 mRNA in the Rat Spinal Cord Following Peripheral Inflammation. FEBS Lett., 1996; 390: 165–169.
10. Yang LC, Marsala M, Yaksh TL; Characterization of Time Course of Spinal Amino Acids, Citrulline and PGE2 Release after Carrageenan/Kaolin-Induced Knee Joint Inflammation: A Chronic Microdialysis Study. Pain, 1996; 67: 345–354.
11. Uda R, Horiguchi S, Ito S, Hyodo M, Hayaishi O. Nociceptive Effects Induced by Intrathecal Administration of Prostaglandin D2, E2, or F2 Alpha to Conscious Mice. Brain Res., 1990; 510: 26–32.
12. Malmberg AB, Yaksh TL; Antinociceptive Actions of Spinal Nonsteroidal Anti-Inflammatory Agents on the Formalin Test in the Rat. J Pharmacol Exp Ther., 1992; 263: 136–146.
13. Chapman V, Dickenson AH; The Spinal and Peripheral Roles of Bradykinin and Prostaglandins in Nociceptive Processing in the Rat. Eur J Pharmacol., 1992; 219: 427–33.
14. Matsumoto M, Inoue M, Ueda H; NSAID Zaltoprofen Possesses Novel Anti-Nociceptive m Mechanism through Blockage of B2-type Bradykinin Receptor in Nerve Endings. Neurosci Lett., 2006; 397: 249–253.
15. Lahdenpaa E, Niskanen M, Yliruusi J; Crushing Strength, Disintegration Time, and Weight Variation of Tablets Compressed from Three Avicel PH Grades and Their Mixtures. Eur. J. Pharm. Biopharm., 1997; 43: 315–322.
16. Li JZ, Rekhi GS, Augsburger LL, Shangraw RF; The Role of Intra- and Extragranular Microcrystalline Cellulose in Tablet Dissolution. Pharm. Dev. Tech., 1996; 1 (4): 343–355.
17. Sun C, Grant DJW; Effect of Initial Particle Size on the Tableting Properties of L-Lysine Monohydrochloride Dihydrate Powder. Int. J. Pharm., 2001; 215: 221–228.
18. Tsai T, Wu JS, Ho HO, Sheu MT; Modification of Physical Characteristics of Microcrystalline Cellulose by Codrying with b-Cyclodextrins, J. Pharm. Sci., 1998; (1): 117–122.
19. Obae K, Iijima H, Imada K; Morphological Effect of Microcrystalline Cellulose Particles on Tablet Tensile Strength. Int. J. Pharm., 1999; 182: 155–164.
20. Hwang R, Peck GR; Systematic Evaluation of the Compression and Tablet Characteristics of Various Types of Microcrystalline Cellulose, Pharm. Technol., 2001; 25(3): 112–132.
21. Heng PWS, Koo OMY; A Study of the Effect of the Physical Characteristics of Microcrystalline Cellulose on Performance in Extrusion Spheronization. Pharm. Res., 2001; 18(4): 480–487.
22. Edge S, Steele DF, Tobyn MJ, Staniforth JN, Chen A; Directional Bonding in Compacted Microcrystalline Cellulose. Drug. Dev. Ind. Pharm., 2001; 27 (7): 613–621.
23. Amidon GE, Houghton ME; Effect of Moisture on the Mechanical and Powder-Flow Properties of Microcrystalline Cellulose. Pharm. Res., 1995; 12(6): 923–929.
24. Patel NK, Upadhyay AH, Bergum JS, Reier GE; An Evaluation of Microcrystalline Cellulose and Lactose Excipients Using an Instrumented Single-Station Tablet Press. Int. J. Pharm., 1994; 110: 203–210.
25. Sixsmith D; Effect of Compression on Some Physical Properties of Microcrystalline Cellulose Powders. J. Pharm. Pharmac., 1977; 29(1): 33–36.
26. Jani GK, Goswami JM, Prajapati VD; Studies on Formulation and Evaluation of New Superdisintegrants for Dispersible Tablets. Int. J. Pharm. Expt., 2005; 2: 37-43.
27. Carr RL; Evaluating Flow Properties of Solids. Chem. Eng., 1965; 72: 163–168.
28. McKenna A, McCafferty DF; Effect of Particle Size on the Compaction Mechanism and Tensile Strength of Tablets. J. Pharm. Pharmac., 1982; 34: 347–351.
29. Akihiko I, Masayasu S; Development of Oral Dosage Form for Elderly Patients: Use of Agar as Base of Rapidly Disintegrating Tablets. Chem. Pharm Bull., 1996; 45: 2132-2136.

30. Ohwoavworhua F, Adelakun T; Phosphoric acid-mediated depolymerisation and decrystallization of a-Cellulose Obtained from Corn Cob: Preparation of Low Crystallinity Cellulose and Some Physicochemical Properties. Tropical journal of Pharmaceutical Research, 2004; 4(2): 509-516.
31. Bultman JM; Multiple Compaction of Microcrystalline Cellulose in a Roller Compactor. Eur. J. Pharm. Biopharm., 2002; 54: 59–64.
32. Mashadi AB, Newton JM; Assessment of the Mechanical Properties of Compacted Sorbitol. Instant. J. Pharm. Pharmacol., 1987; 39: 67.
33. Hancock BC, Christensen K, Clas SD; Microscale Measurement of the Mechanical Properties of Compressed Pharmaceutical Powders, Part 1: The Elasticity and Fracture Behavior of Microcrystalline Cellulose. Int. J. Pharm., 2000; 209: 27–35.
34. Lachman L, Lieberman HA, Kanig JL;The Theory and Practice of Industrial Pharmacy. 3rd edition, Varghese Publishing House, Bombay. 1987: 294, 336, 413.
35. Lieberman HA, Lachman L, Schwartz JB; Pharmaceutical Dosage Forms, 2nd edition, Marcel Dekker Inc, New York.1989; 1: 195-229.
36. Shoukri RA, Ahmed IS, Shamma RN; *In vitro* and *in vivo* Evaluation of Nimesulide Lyophilized Orally Disintegrating Tablets. European Journal of Pharmaceutics and Biopharmaceutics, 2009; 73: 162–171.
37. Tejakrishna M ,V.Sai Kishore,K.V.S.Prasada Rao ,B.Sudheer, Formulation and Evaluation of Mucoadhesive Microbeads of Glimepiride, Scholars Academic Journal of Pharmacy, 2013; 2(3):199-208.