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Research Article

Fabrication of Ketoprofen Controlled-release Tablets using Biopolymeric Hydrophilic Matrices: *In-Vitro* Studies

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Abstract: Ketoprofen is propionic acid derivative and belongs to the Non-Steroidal anti-inflammatory group of drugs. Due to the short half-life, dosage frequency, patient non-compliance and side effects such as gastrointestinal disturbance, peptic ulceration and gastro intestinal bleeding, it is considered to be good candidate for formulation into controlled release dosage forms. Directly compressed controlled released (CR) tablets using Acrylic acid derivatives were prepared and evaluated. *In-Vitro* Physicochemical assessment of the formulated tablets were performed using different physicochemical, dimensional and quality control tests such as weight variation, thickness and diameter, hardness test, friability test, content uniformity, disintegration and dissolution testing. Results of all these tests were formed within acceptable range. The effect of carbomer polymers on the tablet characteristics, drug release rates, release patterns and release kinetics were investigated. The F2-metric technique was applied to compare dissolution profiles of ketoprofen and carbopol tablets with ketoprofen SR-tablets taken as standard preparation. Acrylic acid derivatives when used as polymers resulted in an extended release profile of about 12 h. Using Higuchi's model and the Korsmeyer equation, the drug release mechanism from the tablets was found to be an anomalous type involving diffusion and erosion. Controlled-release Ketoprofen tablets appear to be a good choice for the symptomatic treatment of rheumatoid arthritis and osteoarthritis. Convenient once-daily administration may help improve patients' compliance.

Keywords: Ketoprofen, carbopol, controlled release

1. INTRODUCTION

The disease eradication by humankind involves continuous efforts and struggles. Drug delivery refers to the administration of active pharmaceutical ingredients to attain a therapeutic or pharmacological effect in humans or animals [1]. The primary concern of the drug delivery is to guide the appropriate right concentration of the pharmaceutical ingredient at the right target site for right period of time. For this purpose, different drug delivery systems are developed to achieve a safe and effective drug concentration in body tissues.

Different dosage forms like tablets, capsules, injectables, suppositories, syrups, creams, gels etc. have been employed to deliver drug to patient for the management of either acute illness or chronic diseases for many decades. However, it is prerequisite to administer multiple doses of such dosage forms per day in order to keep the drug level within the established threshold of safety. But, the result may be blood level oscillations due to multiple dosing leading to reduced efficacy and toxicity. Therefore, such factors are vulnerable to the emergence of controlled delivery system [2].

The active agents can be released from a

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delivery system by three basic mechanisms: a) diffusion; b) degradation and c) swelling followed by diffusion. These mechanisms may occur alone or in combination.

Biodegradable polymers have attracted huge attention recently and are the major focus of research efforts. Ketoprofen is NSAID, anionic in nature and recommended for counteracting inflammatory disorders [3]. Ketoprofen is approximately 160 times more potent as an anti-inflammatory agent than that of aspirin [4]. It is odorless, white crystalline powder having sharp bitter taste. Its melting point ranges from 94 to 97 ^{0}C. In the water it is either slightly or completely insoluble but shows free solubility in ether, benzene, chloroform, acetone and ethanol which are organic solvents [5, 6].

Polymer is a compound or macromolecule obtained by the union of wide range of monomer units [7]. The chemistry as well as the assembly of the monomers dictates the chemical reactivity as well as polymeric properties [8]. Considerable interest has been developed to incorporate carbopol in numerous pharmaceutical applications as an excipient [9]. They are fit for direct compression owing to their strong binding behavior and improved compressibility. Carbopol polymers first of all beautified the scientific literature in 1955. They are described as polymers containing acrylic acid and cross linked with sucrose or allylpenta erythritol. All members of the carbopol family are made up of acrylic acids building blocks. However, cross-link density and presence of co-monomer is a point of differentiation between them [10].

2. MATERIALS AND METHODS

2.1. Reagents and Chemicals

Ketoprofen (Sanofi-Aventis Pharmaceutical company, Pakistan); Profenid SR® Ketoprofen (200 mg tablets) market brand by Aventis Pharmaceutical Company, Islamabad, Pakistan; NaOH and Monobasic potassium phosphate (KH_2PO_4) (Merck, Germany); magnesium Stearate, Lactose (BDH Chemical Ltd, Pool England); Carbopol 934P NF and Carbopol 971P NF, Hydroxypropyl methyl cellulose (HPMC K100M) (Dow Chemical Co., Midland USA); Starch and Carboxy methyl cellulose (CMC) (Merck, Germany).

2.2. Instruments

Electronic Balance Model No,AX-200(Shimadzu, Japan), Pharma Test Dissolution Apparatus (PTWS-11/P, TPT Germany), UV-Visible Spectrophotometer Model No. 1601 (Shimadzu, Japan), pH-meter (Denver, USA), Syringes (Otsuka Pakistan), Beakers, Test tubes and Volumetric Flasks (Pyrex, Japan), Single Punch Machine Model#AR 400 (Erweka GMBH, Germany), Hardness tester (Erweka, Germany). Fraibilator (Roche, Germany), Verniar caliper (Germany), Vacuum filter assembly (Sartorius Goettingen, Germany), Whatman filter paper (Whatman, Germany), Magnetic stirrer (Velp Scientica, Germany), Particle scanning distribution size analyzer (Horiba LA-300, Japan), Shaking water bath (Shel Lab 1217-2E, USA), DSC instrument (Mettler Toledo DSC 822e Greifensee, Switzerland), and Stability Chamber (Ti-Sc-THH-07-0400 Faisalabad, Pakistan).

2.3. Determination of Purity Profile of Ketoprofen

The sample was subjected to percentage purity test before formulation of matrix tablets and the results were compared with standard Ketoprofen supplied by Sanofi-Aventis Pharmaceutical Company, Islamabad, Pakistan. For this purpose, 50mg of Ketoprofen was taken and appropriate volume of Phosphate buffer of pH 7.4 was added to make the 100 mL solution. From this solution, 1mL was diluted to get 10 mL. Then, using UV/Visible double beam spectrophotometer, the absorbance of Ketoprofen was noted at 258nm wavelength. The percentage purity was determined as follows:

$$\%\text{age purity} = \times 100$$

Where, std= standard, W= weight

2.4. Powder's Rheology

The compressibility and flow-ability of a powder are important processing factors which should be

noted and inspected before the formulation of tablets. Besides operational processing conditions, physicochemical and mechanical properties of powder also have a unique impact on the flow properties. The flow properties of the powder may be influenced by the cohesive attractive forces present between the powder components [10, 12].

2.5. Compressibility Index and Hausner Ratios

Compressibility Index and Hausner ratio were determined by measuring the bulk and taped volume of powder. The Hausner value refers to the tendency of the powder compression. Taped and bulk densities of a powder are used in its calculations [13]. So, apparent or bulk volume (V_o) was calculated by placing the powder up to 100 mL level in a graduated cylinder having a nominal capacity of 250 mL. Then final volume (V_f) was calculated by subjecting the cylinder to strike slowly against flat surface till powder volume shows no subsequent changes. Following equations are used to determine Compressibility Index and Hausner Ratio, respectively:

$$\text{Compressibility Index} = 100\times \frac{V\circ - Vf}{V\circ}$$

$$\text{Hausner Ratio} = \frac{V\circ}{Vf}$$

2.6. Differential Scanning Colorimetry (DSC) Studies

The objective of this study was to determine the interaction of drug with the polymers and excipients.

2.7. Construction of Standard Curve and Calculation of Concentration of Ketoprofen

The standard curve was constructed by plotting the absorbance values of dilutions made, against their respective concentrations.

Concentration of Ketoprofen is determined using regression Equation.

$$Y=MC + B$$

After arranging the above equation we got:

$$C = (Y-B)/M$$

Where Y = absorbance of solution containing Ketoprofen at 258 nm.

M = Slope of the Ketoprofen Standard Curve of known concentrations.

C = Concentration to be calculated.

B = Intercept of the curve.

2.8. Solubility Study

According to Higuchi and Connors different temperatures such as 25°C, 37°C and 40°C, various solvents such as distilled water, phosphate buffer of pH 7.4, 7.2, 6.8 and 0.1 N HCl were used for solubility of Ketoprofen [14]. Adequately weighed quantity (100 mg) of the drug was taken in the volumetric flask of 100 mL capacity and volume was made up to 100 mL.

2.9. Formulation of Ketoprofen Matrix Tablets

Ketoprofen matrices were prepared using (Carbopol, 934P and 971P) as drug controlling polymers. Lactose was used as primary filler whereas CMC, Starch and HPMC were incorporated as co-excipients. They were added in order to check their impact on the release profile and behavior of the drug. Magnesium stearate was added as lubricant. Matrix tablets were prepared at D:P 10:1, 10:2 and 10:3, respectively, by direct compression method. Composition of tablets has been shown in Table 1.

2.10. Tablet Preparation

All the ingredients required for the preparation were weighed with the help of electronic balance (Shimadzu, Japan). These ingredients were mixed together at the selected D: P ratios (10:1, 10:2, 10:3) with excipients and in case of tablets containing co-excipients (CMC, HPMC and Starch). Initially these were mixed geometrically using mortar and pestle and then each powder mixture was passed through a #30-mesh screen in order to achieve thorough mixing. Subsequently, 0.5% w/w magnesium stearate was added as lubricant and each resulting mixture was passed again twice through the same mesh screen. After mixing each powder mixture was directly compressed with the help of single punch

Table 1. Composition of Carbopol 934P NF, 971P NF based Ketoprofen (200 mg) with HPMC containing matrix tablets.

200 mg Ketoprofen -Carbopol 934 P matrices					
10:1	100 mg	10 mg	62.3 mg	1 mg	26.7 mg
10:2	100 mg	20 mg	55.3 mg	1 mg	23.7 mg
10:3	100 mg	30 mg	48.3 mg	1 mg	20.7 mg
200 mg Ketoprofen -Carbopol 971 P matrices					
10:1	100 mg	10 mg	62.3 mg	1 mg	26.7 mg
10:2	100 mg	20 mg	55.3 mg	1 mg	23.7 mg
10:3	100 mg	30 mg	48.3 mg	1 mg	20.7mg

machine, equipped with 8 mm punch and die set. A batch of 400 tablets was prepared 50 tablets of each type, containing main excipient lactose and co-excipients (CMC, HPMC and starch).

2.11. Physical Investigation of Matrix Tablets

Various quality control tests like hardness test, friability test, weight variation and dimensional specifications such as thickness and diameter were performed (14).

2.12. Content Uniformity

From each batch 10 tablets were taken randomly, made them individually in powder form using pestle and mortar. An aliquot of the powder equivalent to 20 mg of the drug was weighed accurately and shifted to a (100 mL) volumetric flask.

2.13. *In-vitro* Drug Release Study

Measurement of drug was performed using USP method 1 (basket method). In this apparatus 6 flasks, each filled up to 900 mL with 0.2 M phosphate buffer of pH 7.2, was used as dissolution medium to study the release rate and pattern of drug from matrices up to 24 hours. The rotating speed was fixed 100rpm and temperature was kept constant at 37±0.5 °C. At pre-decided time intervals (0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, 18, 24 hours), 5mL of sample was taken with the help of syringe consisting of 0.45 µm filters and was analyzed spectrophotometrically at a detection wave length of 258 nm with the help of UV-Visible Spectrophotometer. After each sampling, equal volume of the dissolution medium was added to maintain total volume constant. From the UV absorbance values and a standard Ketoprofen calibration curve, percentage release was calculated. The procedure was performed for all formulations in triplicate.

2.14. Investigation of Drug Release Kinetics

2.14.1. Zero-order Kinetics

Zero-order model is an ideal kinetic model in achieving sustaining action [15]. Following equation represents this model:

$$W = k1t$$

Where, W= the amount of drug release at time= t

k1= the zero-order release rate constant

t= time

2.14.2. First-order Kinetics [16,17]

First-order equation is applicable under sink conditions. The equation is given as follows:

$$\text{In } (100- W) = \text{lnl00-k2t}$$

Where, W= the amount of drug release at time=t

k2= the first order release rate constant

t= time

2.14.3. Hixon Crowel's Model

This model is also known as 'Erosion Model' [18]. This model was proposed by Hixon and Crowel (1931). This equation is given as follows:

(100-w) 1/3 =100 1/3 -k3t

Where, W= the amount of drug release at time=t

k3= Hixon Crowel's constant showing surface volume relationship

t= time

2.14.4. Higuchi's Model [19,20]

This equation has applications to describe the dissolution rates of pharmaceutical dosage forms other than ointments such as modified drug delivery system. Following equation shows the simple form of this model:

$$W = k_4 t^{½}$$

Where, W= the amount of drug release at time= t

k4= Higuchi dissolution rate constant

t= time

2.15. Applying the Similarity (F2) Factor for Dissolution Equivalency

Similarity factor (f_2) was proposed to compare dissolution profiles and was adopted by FDA as an assessment criterion of similarity b/w two *in-vitro* dissolution profiles. The similarity factor (f_2) is logarithmic reciprocal square root transformation of sum of squared error and is a measurement of the similarity in the percent (%) dissolution b/w the curves [21]. This equation is given:

$$f_2=50\text{Log}\ \{[l=l/nW_t i^n_t(RrT_t)^2]\ ''^{05}xl00\}$$

Where n is the number of pull points, wt is an optional weight factor, Rt is the reference profile at time point t and T_t is the test profile at the same time point. An f_2 value suggests that the test and reference profiles are identical: However, as f_2 value becomes smaller, the dissimilarity b/w release profiles increases [22].

2.16. Studies of Reproducibility and Accelerated Stability

The selected optimized matrices of Ketoprofen were subjected to storage at 25°C and 40°C. For this purpose, stability chamber was used. At 25°C (ambient condition) and at 40°C (accelerated condition) the percent humidity values were 65% and 75% respectively. This test was performed according to the International Commission for Harmonization (ICH) guidelines. After pre-determined intervals (0, 1, 2, 3, 6, 9 and 12 months) Ketoprofen matrices were investigated for appearance and QC tests such as weight variation, friability, content uniformity, dissolution and hardness respectively.

3. RESULTS AND DISCUSSION

3.1. Drug Identity Conformation Studies

Ketoprofen was investigated physically for melting point determination, using British Pharmacopeia, 2007, as reference standard during pre-formulation studies. The melting point of Ketoprofen determined is 96°C which lies within BP limits. The percentage purity of Ketoprofen is 99.81% which is within the BP specified limits.

3.2. Powder's Flow Properties

As shown in the Table 2, the Hausner ratio, compressibility index and angle of repose for pure Ketoprofen are 1.44±0.02, 31±0.02, 49.7±0.03 respectively, representing poor flow properties. To improve the flow properties, 0.5% magnesium stearate was added as lubricating agent.

All the formulations of Ketoprofen blended with magnesium stearate exhibits improved flow properties, as depicted by the values of compressibility index 13.18±0.01 to 15.71±0.01, Hausner ratio 1.12±0.03 to 1.17±0.03 and angle of repose 33.26±0.03 to 36.51±0.02 respectively, in the table 4.1. Addition of magnesium stearate was attributed to produce improvements in the flow of powder samples [24].

3.3. Differential Scanning Colorimetric (DSC) Studies

The DSC peaks of Ketoprofen were found at similar temperature in the homogenized blends of polymers carbopol 934P, 971P and various co-excipients such as lactose, HPMC, CMC, magnesium Stearate and Starch as that of Ketoprofen in pure form and showed no obvious

Table 2. Description of flow behavior of pure Ketoprofen and carbopol 971P NF, 934P NF based formulations.

S. No.	Formulation	D:P Ratio	Co-excipients	Compressibility Index	Hausner Ratio	Angle of Repose
1	Pure Ketoprofen	-	-	31±0.02	1.44±0.02	49.7±0.03
2	Carbopol 971	10:1	Nil	13.88±0.01	1.16±0.04	36.01±0.02
3	Carbopol 971	10:1	CMC	14.21±0.03	1.16±0.02	34.71±0.04
4	Carbopol 971	10:1	Starch	13.61±0.04	1.14±0.01	33.91±0.02
5	Carbopol 971	10:1	HPMC	15.01±0.01	1.17±0.03	35.46±0.03
6	Carbopol 971	10:2	Nil	13.18±0.02	1.14±0.01	34.31±0.01
7	Carbopol 971	10:2	CMC	14.56±0.01	1.15±0.03	35.74±0.02
8	Carbopol 971	10:2	Starch	13.46±0.04	1.16±0.02	34.01±0.02
9	Carbopol 971	10:2	HPMC	14.51±0.01	1.14±0.01	35.16±0.03
10	Carbopol 971	10:3	Nil	13.18±0.01	1.13±0.04	36.31±0.01
11	Carbopol 971	10:3	CMC	14.29±0.03	1.16±0.02	35.11±0.04
12	Carbopol 971	10:3	Starch	13.33±0.04	1.14±0.01	36.09±0.02
13	Carbopol 971	10:3	HPMC	14.71±0.01	1.17±0.03	34.16±0.03
14	Carbopol 934	10:1	Nil	13.18±0.01	1.12±0.04	35.42±0.02
15	Carbopol 934	10:1	CMC	14.81±0.03	1.13±0.02	34.01±0.04
16	Carbopol 934	10:1	Starch	13.89±0.04	1.16±0.01	34.31±0.02
17	Carbopol 934	10:1	HPMC	15.71±0.01	1.17±0.03	33.26±0.03
18	Carbopol 934	10:2	Nil	13.28±0.01	1.16±0.04	35.41±0.02
19	Carbopol 934	10:2	CMC	14.39±0.03	1.16±0.02	34.57±0.04
20	Carbopol 934	10:2	Starch	13.83±0.04	1.15±0.01	34.51±0.02
21	Carbopol 934	10:2	HPMC	15.63±0.01	1.12±0.03	36.06±0.03
22	Carbopol 934	10:3	Nil	14.08±0.01	1.13±0.04	34.01±0.02
23	Carbopol 934	10:3	CMC	14.22±0.03	1.16±0.01	33.49±0.04
24	Carbopol 934	10:3	Starch	13.69±0.04	1.13±0.01	34.65±0.02
25	Carbopol 934	10:3	HPMC	13.68±0.01	1.15±0.04	36.51±0.02

change with respect to Ketoprofen in pure form as shown in Fig. 1 and 2. Thus, no possible chemical interaction was found [24-26].

3.4. Solubility Studies

Fig. 3 describes the results of solubility studies of Ketoprofen in different solvents such as distilled water, phosphate buffer solutions (pH 7.4, 7.2 and 6.8) and 0.1 N HCl solutions at various temperatures such as 40^{o}C, 37^{o}C and 25^{o}C. It is cleared from the fig 4.6 that the solubility of the drug is elevated in phosphate buffer solution of pH 7.4, whereas other solvents exhibit lower solubility profiles.

Since, ionization constant of Ketoprofen is 4.6 which means it is weakly acidic drug and the solubility of such type of drugs is usually pH dependent. That is why, this elevated solubility of Ketoprofen is attributed to weak acidic nature of the drug and at higher pH value, the solubility of Ketoprofen is also high.

Moreover, it was also found that an increase in temperature also increased the solubility of Ketoprofen in all solvents in different way, as shown in the Fig 6. This enhanced solubility may be due to the absorption of heat because the most of the drugs do possess heat of solution values in positive integers that result in an extended solubility as the temperature of the system is increased. Our findings in this regard show compliance with Loyd et al. [26].

3.5. Physico-Chemical Assessment of Matrix Tablets

The results of average hardness, thickness and diameter, friability, weight variation and content uniformity of the Ketoprofen matrices are shown in the Table 3. When investigated, all the

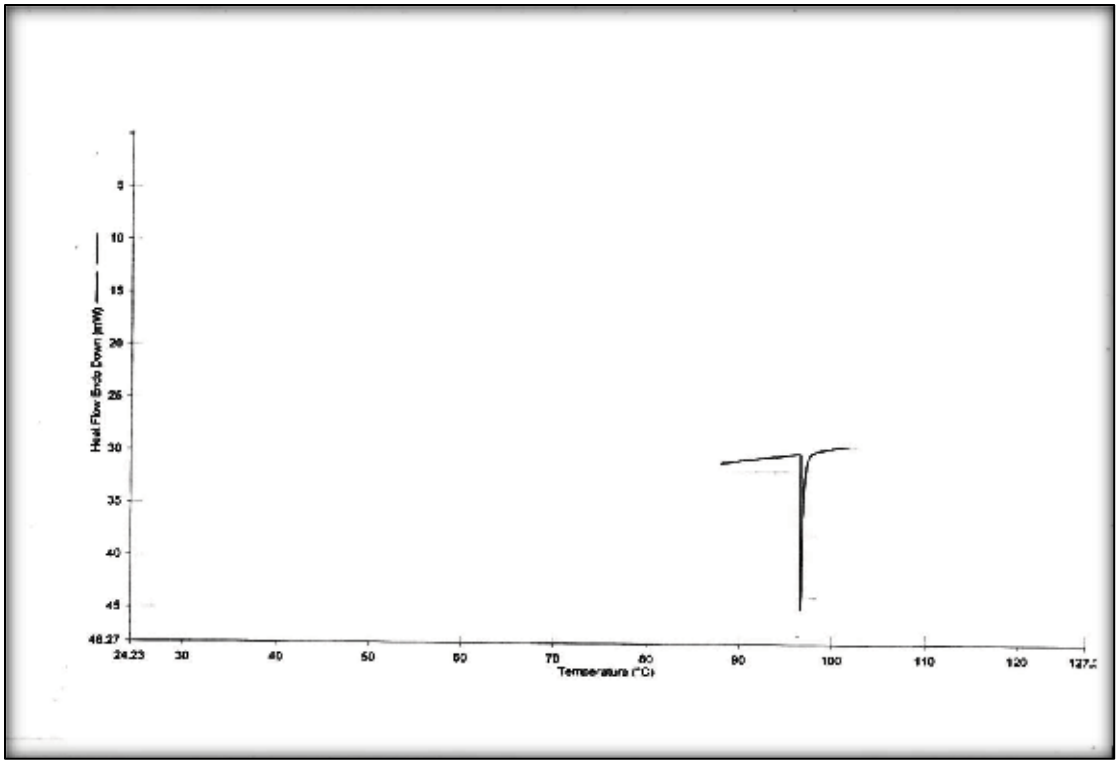

Fig 1. Pure Ketoprofen DSC thermogram.

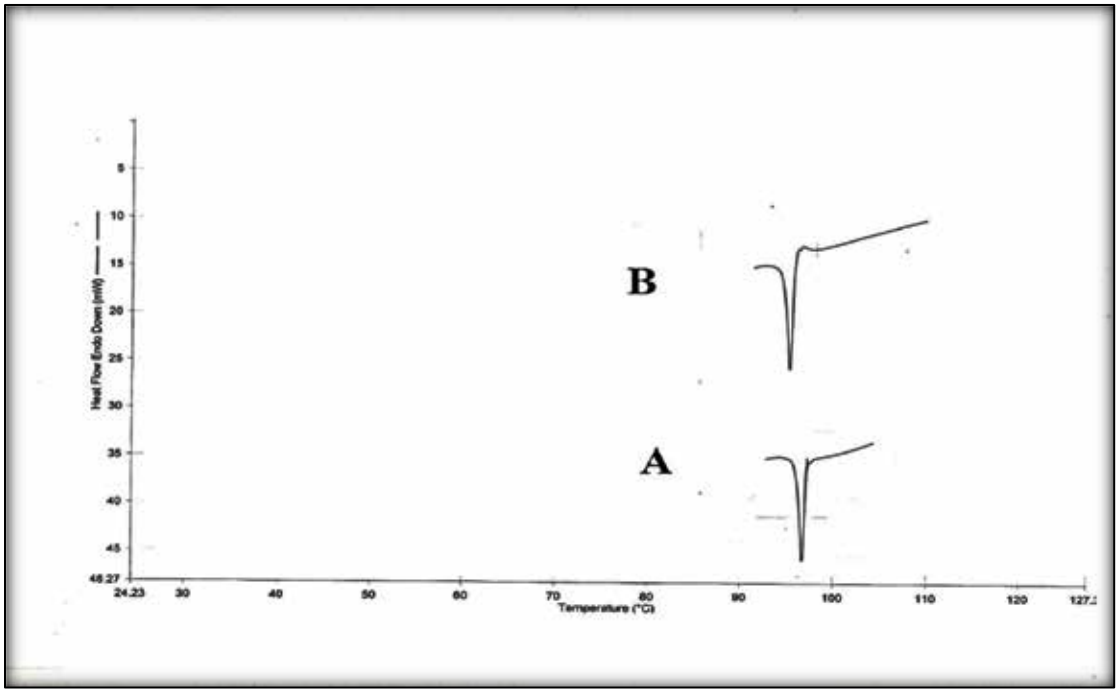

Fig. 2. Ketoprofen with carbopol 971P NF (A), 934P NF (B) DSC thermogram.

Table 3. Physicochemical characteristics of Ketoprofen controlled release matrix formulations.

S. No.	Polymer	D:P Ratio	Co-exicipient	Wt variation (mg) n=20 (Mean ±SD)	Hardness (Kg/cm^3) n=10 (Mean ±SD)	Friability (%) n=3 (Mean ±SD)	Thickness (mm) n=20 (Mean ±SD)	Diameter (mm) n=20 (Mean ±SD)	Drug content (%) n=3 (Mean ±SD)
1	Carbopol 971	10:1	Nil	199.02±0.401	6.99±0.03	0.18±0.04	3.53±0.03	7.93±0.27	100.01±1.35
2	Carbopol 971	10:1	CMC	199.01±0.325	7.08±0.08	0.21±0.06	3.56±0.06	7.91±0.12	99.77±2.02
3	Carbopol 971	10:1	Starch	199.03±0.299	7.11±0.01	0.15±0.01	3.48±0.04	7.97±0.28	98.96±1.68
4	Carbopol 971	10:1	HPMC	200.01±0.201	6.95±0.08	0.20±0.07	3.47±0.02	7.92±0.22	100.03±1.66
5	Carbopol 971	10:2	Nil	199.9±0.345	6.96±0.05	0.17±0.06	3.53±0.05	7.93±0.21	99.78±2.26
6	Carbopol 971	10:2	CMC	200.02±0.287	7.13±0.01	0.22±0.02	3.47±0.07	7.88±0.22	98.96±1.48
7	Carbopol 971	10:2	Starch	199.02±0.341	7.01±0.05	0.16±0.04	3.56±0.04	7.89±0.27	100.01±1.71
8	Carbopol 971	10:2	HPMC	200.18±0.389	6.99±0.06	0.15±0.09	3.51±0.03	7.87±0.15	99.69±2.14
9	Carbopol 971	10:3	Nil	200.05±0.326	7.01±0.04	0.22±0.02	3.56±0.02	7.96±0.15	99.01±1.88
10	Carbopol 971	10:3	CMC	199.91±0.312	6.94±0.05	0.18±0.01	3.57±0.07	7.93±0.11	100.03±1.36
11	Carbopol 971	10:3	Starch	198.97±0.351	7.16±0.03	0.16±0.04	3.58±0.04	7.98±0.23	99.78±2.29
12	Carbopol 971	10:3	HPMC	199.1±0.422	6.97±0.07	0.20±0.07	3.49±0.07	7.90±0.02	98.99±1.48
13	Carbopol 934	10:1	Nil	200.01±0.351	7.07±0.05	0.16±0.02	3.51±0.05	7.92±0.09	100.05±1.26
14	Carbopol 934	10:1	CMC	200.03±0.325	6.88±0.06	0.21±0.06	3.46±0.02	7.96±0.25	99.37±2.29
15	Carbopol 934	10:1	Starch	201.11±0.289	7.11±0.07	0.15±0.09	3.56±0.04	7.93±0.21	98.96±1.91
16	Carbopol 934	10:1	HPMC	200.75±0.387	7.08±0.08	0.21±0.07	3.45±0.01	7.92±0.27	100.02±1.36
17	Carbopol 934	10:2	Nil	199.10±0.225	6.97±0.03	0.19±0.02	3.52±0.03	7.88±0.21	99.37±2.29
18	Carbopol 934	10:2	CMC	200.02±0.263	6.90±0.02	0.20±0.02	3.51±0.06	7.86±0.16	98.98±2.18
19	Carbopol 934	10:2	Starch	200.00±0.360	7.06±0.04	0.17±0.07	3.51±0.04	7.85±0.11	100.03±1.06
20	Carbopol 934	10:2	HPMC	200.21±0.291	6.96±0.05	0.19±0.02	3.44±0.03	7.91±0.19	99.86±2.42
21	Carbopol 934	10:3	Nil	200.38±0.256	7.12±0.06	0.18±0.03	3.50±0.02	7.93±0.17	98.95±1.91
22	Carbopol 934	10:3	CMC	199.96±0.214	7.01±0.08	0.22±0.09	3.48±0.08	7.91±0.15	100.03±1.21
23	Carbopol 934	10:3	Starch	199.8±0.342	7.03±0.07	0.17±0.02	3.48±0.06	7.90±0.14	99.61±2.02
24	Carbopol 934	10:3	HPMC	199.03±0.311	6.93±0.02	0.16±0.03	3.46±0.07	7.91±0.14	99.49±1.28

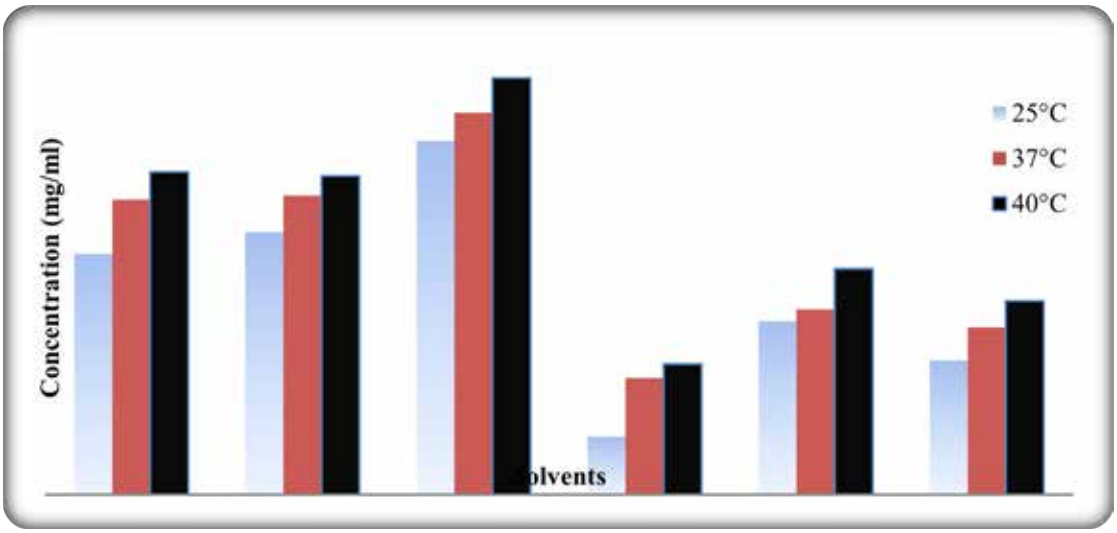

Fig. 3. Ketoprofen Solubility profiles in various solvents at different temperatures.

formulations possessed their results of hardness, thickness and diameter, friability, weight variation and content uniformity within the limits of official compendia (USP and BP).

3.6. In-Vitro Dissolution Study of Directly Compressed Ketoprofen Matrix Tablets

This study was performed to evaluate the release of the drug from matrices containing carbopol 971P NF, 934P NF. Additionally, the influence of concentration of polymer and progressive substitution of lactose with CMC, Starch and HPMC was investigated to describe the release pattern of Ketoprofen from various combinations of matrices.

3.7. The Impact of Polymer Concentration on Ketoprofen Release Rate

Fig. 4-6 depict Ketoprofen % release from matrices containing carbopol 971P NF, 934P NF at drug to polymer ratios of 10:1, 10:2 and 10:3, respectively. It can be observed that more the polymer (Carbopol 971P NF, 934P NF) in the formulation more is the reduction in the drug release rates. This might occur upon contact with water by virtue of the hydration of polymeric matrix as it causes swelling. As a result, tends to close up the micropores in the inflated tablets causing reduction in the drug release from the matrix tablets.

The ability of the carbopol polymers to swell and uptake water is mainly dependent upon the density of cross linking. Carbopol 971P NF, being the most lightly cross linked, possesses few cross link regions to restrain the polymer as a result it opens up easily thus producing maximum swelling and greater water uptake as compared to the carbopol 934P NF, which is highly cross linked and cross linking regions resist the polymer to open up easily thus producing lesser swelling [27]. Moreover, an increased level of carbomer not only yields a decreased drug release rate but also results in the linearization of the drug release curve leading to a shift towards a swelling controlled mechanism (case II mechanism). Hydration of the polymer produces swollen tablets, decreasing its glass transition temperature (Tg) to the temperature of the dissolution medium. This might be evident microscopically as a relaxation phenomenon of polymer chains that produced as a result of dissolution medium induced stresses, causing the polymer chains to start gyrating. The ultimate result is swelling due to the increase radius of gyration and end to end distances of the polymer chains.

There was an obvious increase in the molecular volume of the hydrated polymer which reduces the free volume due to the presence of micropores. This response may manifest itself as a shift in the drug release mechanism. Our results also confirm the findings of others researchers who have studied the effects of concentration of polymers on dissolution kinetics [27, 28].

3.8. Ketoprofen Release Kinetics Investigation

Tables 4 and 5 present statistics of various parameters of different kinetic models to test the formulations of Ketoprofen for the release profiles

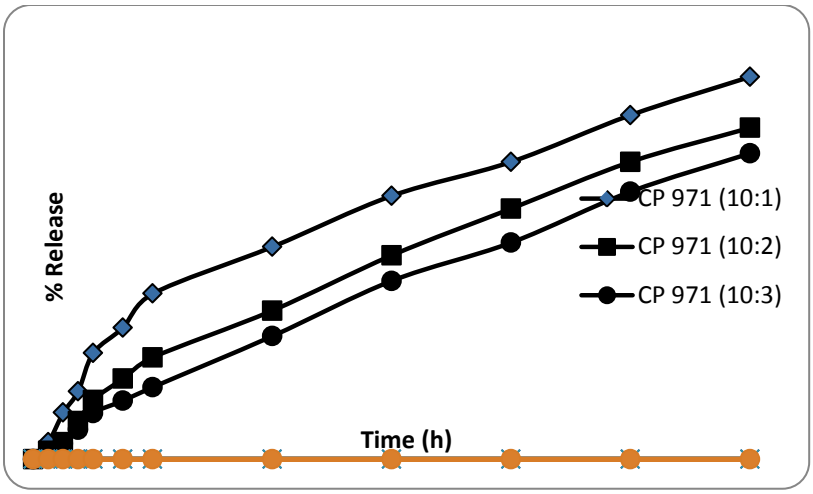

Fig 4. Carbopol 971P NF based Ketoprofen matrices release profile at different D: P ratios.

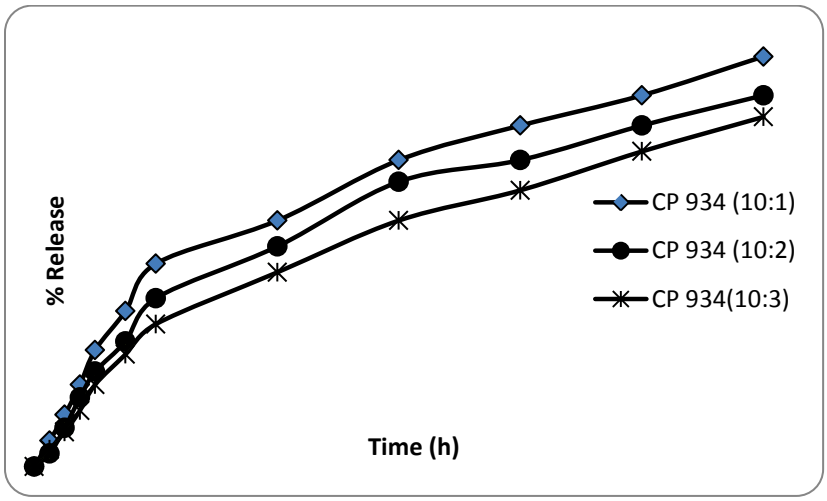

Fig 5. Carbopol 934P NF based Ketoprofen matrices release profile at different D: P ratios.

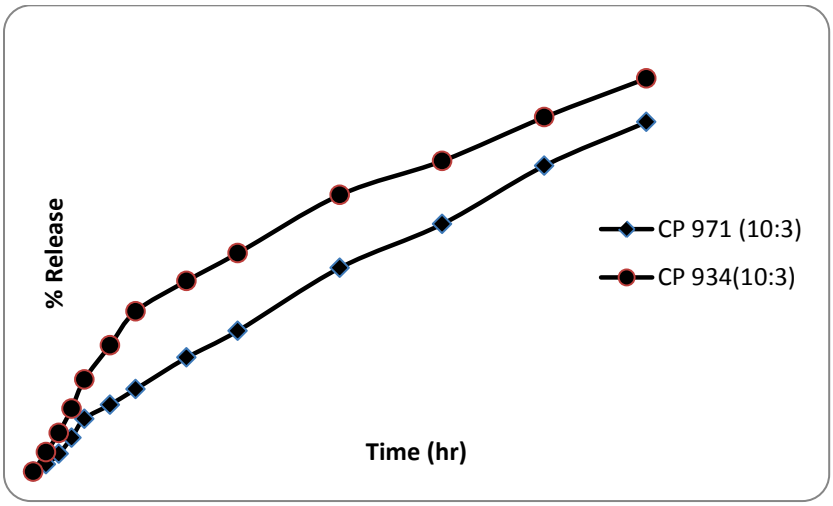

Fig 6. Comparative Release profiles of Ketoprofen from Carbopol 971P NF and 934P NF matrix tablets with D: P Ratio 10:3.

Table 4. Various kinetic models employed to establish the release profile of CR matrix tablets of Ketoprofen comprising of carbopol 971P NF, 934P NF, (mean±SD of three determinations).

Formulation	W=k1t		(100-w)=ln100-k2t		$(100-w)^{1/3}=100^{1/3}$-k3t		$W=k4t^{1/2}$		$Mt/m\infty=k5t^n$		n
	K_1±SD	r_1	K_2±SD	r_2	K_3±SD	r_3	K_4±SD	r_4	K_5±SD	r_5	
Ketoprofen-Carbopol 971											
10:1	7.32±2.43	0.918	0.131±0.01	0.967	0.174±0.043	0.954	6.664±2.56	0.921	0.052±0.221	0.941	0.722
10:2	5.62±1.87	0.928	0.981±0.02	0.977	0.133±0.021	0.958	5.863±3.11	0.943	0.171±0.451	0.989	0.765
10:3	4.76±0.78	0.991	0.073±0.01	0.991	0.088±0.022	0.992	4.448±1.89	0.999	0.559±1.31	0.999	0.849
Ketoprofen-Carbopol 934											
10:1	7.992±4.81	0.908	0.177±0.11	0.917	0.279±0.0461	0.973	6.831±4.16	0.934	0.049±0.021	0.957	0.581
10:2	6.871±3.73	0.957	1.13±0.023	0.986	1.431±0.029	0.986	7.161±2.19	0.977	0.176±0.151	0.986	0.765
10:3	4.71±0.782	0.993	0.088±0.01	0.993	0.194±0.021	0.997	4.988±1.09	0.994	0.479±1.31	0.999	0.846

Table 5. Various kinetic models employed to establish the release profile of CR matrix tablets of Ketoprofen comprising of carbopol 971P NF, 934P NF and HPMC K100M (mean±SD) n=3.

Formulation	W=k1t		(100-w)=ln100-k2t		$(100-w)^{1/3}=100^{1/3}$-k3t		$W=k4t^{1/2}$		$Mt/m\infty=k5t^n$		n
	K_1±SD	r_1	K_2±SD	r_2	K_3±SD	r_3	K_4±SD	r_4	K_5±SD	r_5	
Ketoprofen-Carbopol 971 and HPMC											
10:3	7.163±4.391	0.962	0.183±0.091	0.802	0.209±0.061	0.8861	7.038±4.890	0.9441	0.036±0.082	0.9951	0.714
Ketoprofen-Carbopol 934 and HPMC											
10:3	9.691±10.351	0.7993	0.364±0.223	0.645	0.357±0.174	0.7342	8.121±9.09	0.778	0.011±0.033	0.971	0.593

Table 6. Various kinetic models employed to establish the release profile of CR matrix tablets of Ketoprofen comprising of carbopol 971P NF, 934P NF and co-excipient CMC, (mean±SD) n=3.

Formulation	W=k1t		(100-w)=ln100-k2t		$(100-w)^{1/3}=100^{1/3}$-k3t		$W=k4t^{1/2}$		$Mt/m\infty=k5t^n$		n
	K_1±SD	r_1	K_2±SD	r_2	K_3±SD	r_3	K_4±SD	r_4	K_5±SD	r_5	
Ketoprofen-Carbopol 971 and CMC											
10:3	2.234±2.18	0.0177	1.371±0.88	0.038	1.183±1.72	0.006	1.408±1.89	0.083	0.00±0.00	0.721	0.021
Ketoprofen-Carbopol 934 and CMC											
10:3	2.244±2.18	0.0167	1.364±0.76	0.048	1.363±1.78	0.004	1.331±1.06	0.081	0.00±0.00	0.701	0.026

Table 7. Various kinetic models employed to establish the release profile of CR matrix tablets of Ketoprofen comprising of carbopol 971P NF, 934P NF and Starch as co-excipient (mean±SD) n=3.

Formulation	W=k1t		(100-w)=ln100-k2t		$(100-w)^{1/3}=100^{1/3}$-k3t		$W=k4t^{1/2}$		$Mt/m\infty=k5t^n$		n
	K_1±SD	r_1	K_2±SD	r_2	K_3±SD	r_3	K_4±SD	r_4	K_5±SD	r_5	
Ketoprofen-Carbopol 971 and Starch											
10:3	6.763±0.71	0.9381	0.073±0.01	0.991	0.088±0.022	0.992	4.448±1.89	0.999	0.559±1.31	0.999	0.743
Ketoprofen-Carbopol 934 and Starch											
10:3	3.61±2.782	0.1932	1.181±1.01	0.0063	1.094±1.021	0.0577	2.534±2.09	0.184	0.000±0.00	0.769	0.041

from tablets containing carbopol 971P NF, 934P NF polymers at various D: P ratios with or without co-excipients (HPMC K100M, CMC and Starch). Linear relation was observed for all the formulations based on the kinetic models. All the kinetic models from the equations (1 to 5) suitably fitted the drug release data but Ketoprofen percentage release data best fitted to the equation 5 (Power law equation). Carbopol 971P NF and 934P NF at D: P ratio of 10:3 respectively exhibited maximum 'r' values with excellent linear relation.

In case of co-excipients containing formulation, HPMC K100M formulations at D: P ratio of 10:3 showed linear relation when the values of various parameters were put to equations 1 to 5. Anyhow, CMC and Starch oriented formulations showed marked variation in their release mechanism. When the data was fitted to equations 1 to 5, non-linear relationship was observed having minimal 'r' values.

It is evident that most of the formulations exhibit anomalous, non-Fickian release mechanism as the values of 'n' ranges from 0.581 and 0.849 (Table 6 and 7), which means that the release mechanism is entirely diffusion based followed by enhanced swelling and erosion. Some of the preparations exhibited smaller 'n' values which describe partial diffusion through water filled pores and swelled matrix [29].

3.9. Accelerated Stability and Reproducibility Study

Ketoprofen matrix formulations containing carbopol 971P NF, 934P NF at drug to polymer ratio 10:3 were regarded as the optimum formulations for the study of stability. For this purpose, these formulations were kept at both room as well as accelerated temperatures, (25^{o}C, RH=65%, ambient conditions; 40^{o}C, RH=75%) for 1 year.

The matrices were analyzed for appearance, weight variation, hardness, content uniformity, friability and dissolution profile at pre-selected time frames i.e. 0, 1, 2, 3, 6, 9, & 12 months. The tables 8 and 9 show that no profound changes were noticed in weight variation (200.1±0.8, 200±1, 199±0.141, 200±0.112, 200.05±0.24, 200.1±0.111, 200.65±0.76) at room temperature, hardness (7.13±0.091, 7.14±0.045, 7.14±0.066, 7.15±0.013, 7.16±0.011, 7.17±0.031, 7.17±0.71), %drug content in ambient conditions (99.99±1, 100.01±2, 100.09±1, 99.79±1, 99.61±2, 99.55±1, 99±1), %friability (0.14±0.02, 0.14±0.01, 0.15±0.03, 0.14±0.03, 0.16±0.07, 0.16±0.03, 0.16±0.02), %drug release (94.8±0.12, 96.6±0.22, 94.5±0.19, 94.5±0.12, 94.1±0.11, 94±0.33, 93.8±0.142) and whitish appearance, tested at time frames cited as above. Similar results were noted upon storage at accelerated temperature and no profound changes were reported at accelerated temperature on weight variation (200.01±0.3, 200±0.45, 199±0.23, 200±0.109, 200±0.24, 200.4±0.19, 200.5±0.71), hardness (7.13±0.091, 7.13±0.015, 7.14±0.036, 7.15±0.019, 7.16±0.017, 7.17±0.023, 7.17±0.034), %drug content (100.93±1, 100.21±2, 100.09±1, 99.91±1, 99.81±2, 99.65±1, 99.11±2), %friability (0.14±0.02, 0.15±0.02, 0.15±0.01, 0.14±0.05, 0.16±0.02, 0.16±0.04, 0.16±0.01),), %drug release (94.8±0.12, 95.1±0.28, 94.9±0.12, 94.8±0.15, 94.6±0.14, 94.1±0.31, 93.9±0.16) and whitish appearance, tested at zero time which is pre-storage and at 1, 2, 3, 6, 9, and 12 months respectively after storage. Since, no marked variation exists in the percent drug release, thus it can be concluded that controlled release matrices of Ketoprofen were stable, reproducible and reliable.

3.10. Applying the Similarity (F2) Factor for Dissolution Equivalency

The f_2-matric technique was used to compare the different Ketoprofen release profile obtained from Carbopol 971P NF and 934P NF matrices. For this purpose, release profile associated with Ketoprofen SR-Tablets (dilution factor was 2) functioned as a reference profile. Table 10 presents the relevant data. It can be seen that at a D:P ratio of 10:3, all the formulations were significantly different from the reference formulation.

4. CONCLUSIONS

Use of carbopol 971P NF, 934P NF as controlled release agents can enhance the controlled release properties of slightly water soluble drugs; Ketoprofen as carbopol 971P NF, 934P NF can form strong matrices due to their inherently cross linked structure. The drug release can be delayed and controlled by carbopol 971P NF, 934P NF in

Table 8. Stability indicating parameters and appearance after 24 hours for Ketoprofen matrices in ambient conditions (25°C and RH65%).

Reading taken for determination of stability	Drug content (%) n=3 (Mean±SD)	Weight variation test (mg) n=20 (Mean±SD)	Friability test (%) n=3 (Mean±SD)	Hardness test (kg/cm^2) n=10 (Mean±SD)	% Release after 24h n=3 (Mean±SD)	Appearance (colour)
At 0 time (pre storage)	99.99±1	200.1±0.8	0.14±0.02	7.13±0.091	94.8±0.12	Whitish
After 1 month	100.01±2	200±1	0.14±0.01	7.14±0.045	94.6±0.22	Whitish
After 2 month	100.09±1	199±0.141	0.15±0.03	7.14±0.066	94.5±0.19	Whitish
After 3 month	99.79±1	200±0.112	0.14±0.03	7.15±0.013	94.5±0.12	Whitish
After 6 month	99.61±2	200.05±0.24	0.16±0.07	7.16±0.011	94.1±0.11	Whitish
After 9 month	99.55±1	200.1±0.111	0.16±0.03	7.17±0.031	94±0.33	Whitish
After 12 month	99 ±1	200.65±0.76	0.16±0.02	7.17±0.71	93.8±0.142	Whitish

Table 9. Stability indicating parameters and appearance after 24 hours for Ketoprofen matrices in accelerated conditions (40°C and RH75%).

Reading taken for determination of stability	Drug content (%) n=3 (Mean±SD)	Weight variation test (mg) n=20 (Mean±SD)	Friability test (%) n=3 (Mean±SD)	Hardness test (kg/cm^2) n=10 (Mean±SD)	% Release after 24h n=3 (Mean±SD)	Appearance (colour)
At 0 time (pre storage)	100.93±1	200.1±0.3	0.14±0.02	7.13±0.091	94.8±0.12	Whitish
After 1 month	100.21±2	200±0.45	0.15±0.02	7.13±0.015	95.1±0.28	Whitish
After 2 month	100.09±1	199±0.23	0.15±0.01	7.14±0.036	94.9±0.12	Whitish
After 3 month	99.91±1	200±0.109	0.14±0.05	7.15±0.019	94.8±0.15	Whitish
After 6 month	99.81±2	200±0.24	0.16±0.02	7.16±0.017	94.6±0.14	Whitish
After 9 month	99.65±1	200.4±0.19	0.16±0.04	7.17±0.023	94.1±0.31	Whitish
After 12 month	99.11±2	200.5±0.71	0.16±0.01	7.17±0.34	93.9±0.16	Whitish

Table 10. f_2-matric values to establish the equivalency between the Ketoprofen release profiles of 200 mg SR-tablets and carbopol 971P NF, 934P NF matrices.

S. No.	200 mg Ketoprofen SR-tablets as reference	F_2-Matric Values
1	SR-tablets/ Carbopol 934P	24.989
2	SR-tablets/ Carbopol 934P with co-excipient CMC	43.544
3	SR-tablets/ Carbopol 934P with co-excipient HPMC	44.150
4	SR-tablets/ Carbopol 934P with co-excipient Starch	49.174
5	SR-tablets/ Carbopol 971P	38.760
6	SR-tablets/ Carbopol 971P with co-excipient CMC	43.251
7	SR-tablets/ Carbopol 971P with co-excipient HPMC	44.874
8	SR-tablets/ Carbopol 971P with co-excipient Starch	27.427

a concentration dependent manner. Carbopol 971P NF is more efficient than carbopol 934P NF in controlling and expanding the release rates of Ketoprofen.

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