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Research Article

FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF ACECLOFENAC USING HYDROPHILIC MATRIX SYSTEM

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ABSTRACT

The objective of the present study was to develop "once daily" sustained release tablets of Aceclofenac (200mg) by wet granulation using hydrophilic polymer like Hydroxy propyl methyl cellulose K -100. The drug excipient mixtures were subjected to preformulation studies. The tablets were subjected to physicochemical studies, *in- vitro* drug release, kinetic studies and stability studies. FTIR studies shown there was no interaction between drug and polymer. The physicochemical properties of tablets were found within the limits. Aceclofenac is a non steroidal anti-inflammatory agent used in symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis. The drug release from optimized formulations was extended for a period of 24 hrs. The kinetic treatment of selected formulation (F8) showed that the release of drug follows zero order models. The optimized formulations were subjected to stability studies for one month at 45° temperature with RH 75±5% and showed there were no significant changes in drug content, physicochemical parameters and release pattern. Results of the present study indicated the suitability of hydrophilic polymers in the preparation of matrix based sustained release formulation of Aceclofenac.

Keywords: Aceclofenac, Matrix tablets, Sustained release, Wet granulation, Hydroxy Propyl Methyl Cellulose K -100

INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) are considered to be the first-line drugs in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and spondylitis, Aceclofenac is one of them[1]. It is a newer derivative of Diclofenac with low gastrointestinal complications. The short biological half-life (3- 4h) and dosing frequency more than one per day make Aceclofenac an ideal candidate for sustained release. To reduce the frequency of administration and to improve patient compliance, a once-daily sustained release formulation of Aceclofenac is desirable.

Matrix tablets composed of drug and polymer as release retarding material offer the simplest approach in designing a sustained release system. The present study aims to develop sustained release matrix tablets using hydrophilic matrix materials[2], such as HPMC- K 15 and HPMC- K 100 along with drug in varying proportions by wet granulation method. For sustained release systems, the oral route of drug administration has received the most attention as it is natural, uncomplicated, convenient and safer route[3]. Matrix tablets were prepared by either wet granulation or direct compression method. Currently available sustained matrix tablets are generally prepared by wet granulation method. The aim of the present work was to prepare sustained release matrix tablets of Aceclofenac and to study the effect of *in-vitro* release characteristics, kinetics of the prepared formulations and stability studies[10].

MATERIALS

Aceclofenac, Hydroxy propyl methyl cellulose K-100 and, Hydroxyl propyl methyl cellulose K-15 were obtained as gift samples from Arvind Remedies Ltd, Tamil nadu, India. Lactose, Mannitol, Povidone (PVP K-30) were purchased from Unify chemicals, Jothi Aromas and DK Enterprises respectively. Magnesium stearate, Talc and Aesrosil were purchased from S.D.Fine-Chem Limited, Mumbai, India. All other chemicals used were of analytical grade.

METHODS

Preformulation studies

Micromeritic properties

The physical mixtures were prepared by triturating drug and excipients in a dried mortar for 5 min. The angle of repose of Aceclofenac and its Physical mixtures with other excipients were determined by fixed funnel method. The angle of repose, Compressibility index (C.I.), Degree of compression (c) and the Hausner's ratio were calculated[4] using following equations. The result was shown in table no: 1

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

Where, θ =Angle of repose

h=Height of granule above flat surface

r=Radius of circle formed by the granule pile.

$C.I. = \{(\rho t - \rho 0) / \rho t\} \times 100$ ------- (2)

Where, ρt - tapped density, ρ0 - bulk density.

$C = (Ho-Hp / Ho) \times 100$---------- (3)

Where, C - Degree of compression

Ho - height of granule bed in the die before compression.

Hp - height of granule bed in the die at a pressure p.

Hausner's ratio = TBD / LBD ---------- (4)

Where, TBD - Tapped Bulk Densities

LBD - Loose Bulk Density

Drug-excipient compatibility studies

Infrared (IR) spectroscopy was conducted using a FTIR Spectrophotometer (Jasco FT-IR 410) and the spectrum was recorded in the wavelength region of 4000 to 400 cm−1. The procedure consisted of dispersing a sample (drug alone or mixture of drug and excipients) in KBr and compressed into discs by applying a pressure of 5 tons for 5 min in a hydraulic press. The pellet was placed in the light path and the spectrum was obtained.

Preparation of tablets

Tablets weighing 320mg were prepared containing 200 mg of Aceclofenac and Lactose, Mannitol and HPMC K100. Polyvinyl pyrrolidone (2.8%) was used as binder. Magnesium stearate (2.8%) and Talc (1.8%) was added as lubricant prior to compression. Different tablet formulations were prepared by wet granulation technique. All the powders were passed through 24 mesh. Required quantity of drug, diluents and polymers were mixed thoroughly and a sufficient quantity of binding agent was added slowly. After enough cohesiveness was obtained, the mass was sieved through 16 mesh. The granules were dried at 50ºC for 45minuts and were

mixed with talc and magnesium stearate.[9] The tablets were compressed using Mini Press tablet compression machine (Clit jemkey Eng Pvt. Ltd). The different formulations were shown in table no: 2

Evaluation of physical properties of matrix tablets

All prepared matrix tablets were evaluated for uniformity of weight and drug content, as per I.P. Friability was determined using Electro lab friabilator. Hardness was measured by using Pfizer hardness tester. Diameter and thickness were measured by Vernier caliper[5]. The result was shown in table no: 3

Dissolution studies

The in vitro dissolution study was carried out using USP Type II dissolution apparatus. The study was carried out in 900 ml of 0.1N HCl (pH 1.2) for first 2hours and then 900 ml of phosphate buffer (pH 6.8) from 2nd to 24th hr. The dissolution medium was kept in thermostatically controlled water bath, maintained at 37±0.5^{0}C. Basket rotation was adjusted to 50 rpm. At definite intervals, 5 ml sample was withdrawn and analyzed spectrophotometricaly at 274 nm for the drug release. At each time of withdrawal, 5 ml of fresh corresponding medium was replaced into the dissolution flask[6,10,12].

Dissolution characteristics

Present study of selected formulation was carried out on different pH medium (0.1N HCL & 6.8 pH phosphate buffer), hardness (5-6, 6-7Kg/cm^2) and shapes (12/32 biconcave punch, 12/32 depth concave punch, 12/32 flat beveled punch). Each type containing same concentration of the drug (200 mg of Aceclofenac) and polymer.[13]

Kinetic treatment of dissolution data

In order to describe the kinetics of the release process of drug in the selected formulation, zero- order (Qt= Q0 + K0t), first- order (ln Qt = ln Q0 + K1t). Higuchi (Qt =KHt1/2) and Korsmeyer-Peppas (Qt/Q∞= Ktn) models were fitted to the dissolution data of selected formulation (F8), using linear regression analysis. A value of n = 0.5 indicates case I (Fickian) diffusion or square root of time kinetics, 0.5<n<1 anomalous (Non- Fickian) diffusion, n=1 Case –II transport and n>1 Super Case II transport[7].

Stability studies

Accelerated stability study was carried out to observe the effect of temperature and relative humidity on selected formulation (F8), by keeping at 40°± 2°C, in air tight high density polyethylene bottles for three months, at RH 75±5%. Physical evaluation and *in-vitro* drug release was carried out in each month[8].

RESULTS AND DISCUSSION

Micromeritic properties

The results of Micromeritic properties were performed. The results of indicate that the Aceclofenac raw material showing passable flowability with the angle of repose values ranging from 32.25^o to 33.45^o. All granules ready for compression showing fair to good flowability with the angle of repose values ranging from 25.62^o to 29.56^o. According to angle of repose graph readings and are better than that of powder drug. The bulk density, tapped density, compressibility index and Hausner ratio were observed. It reveals that all the formulation blend having good flow characteristics and flow rate than raw material. Degree of compression is characteristic of compression capability of the granules and the results obtained exhibited good compression capability of the granules.

Drug excipient compatibility studies

Drug excipient compatibility studies were carried out by IR spectrophotometer. The IR spectra of pure Aceclofenac and its polymers were shown there was no interaction between drug and polymer.

Evaluation of prepared tablets

The results of physical evaluation of tablets were given in Table no: 2. The tablets of different batches were found uniform with respect to hardness within the range of 5-7 kg/cm^2. Another measure of a tablet's strength is friability. Conventional compressed tablets that lose Less than 1% of their weight are generally considered acceptable. The diameter of all Diameter of all formulation was in the range of 9.57- 9.58 mm. In weight variation test, the pharmacopoeial limit for percentage deviation for tablets of more than 250 mg is ±5% and all the formulations were found to comply with the specifications given in I.P. for weight variation test. Good uniformity in drug content was found among the formulations, and percentage of drug content was more than 95%. All the tablet formulations showed acceptable pharmaco technical properties.

***In - vitro* drug release study**

The release profile of Aceclofenac from different batches of formulated matrix tablets were illustrated in Table no:4 and plotted in Figure no:1. All the formulations showed very low drug release in 0.1N HCl (pH 1.2). This was due to the very low solubility of Aceclofenac at pH 1.2 formulation (F1) with less amount HPMC- K15 gives 100% release in 4th hr. When increases the polymer ratio in F2 release is retarding. On combination of HPMC- K15 & HPMC- K100 in F3 & F4, better release got at the end of 24th hour (86.47% & 87.44%) respectively. When only HPMC-K100 used, in F5-F8 above 90% achieved in at end of 24th hr. the final formula (F8) complies with all the release limits and giving 95.72% in 24th hr. Hence formulation 8 was selected as best formula. Formulation F8 containing HPMC- K100was found to release the drug in sustained manner up to 24 hour and was considered optimum for stability studies.

***In - vitro* Dissolution characteristics**

pH challenge studies

From this data the rate of drug release in 0.1 NHCL and phosphate buffer pH 6.8, The release of the drug is faster in phosphate buffer (pH 6.8) than 0.1 N HCL medium.

Effect of shape on dissolution rate for formulation (F8)

From the obtained data reveled that the rate of drug release of 12/32 Bi convex tablets shown maximum release. 12/32 Flat beveled tablet was initially fast but it slowed down. In the case of 12/32 depth concave tablet, the rate of drug release was slowed down.

Effect of hardness on dissolution rate for formulation (F8)

The rate of drug release in case of hardness 6-7 kg/cm2 is slow, in comparison to that of 5-6kg/cm2 hardness.

Stability studies

The results of accelerated stability studies carried out according to ICH guidelines indicated that the tablets did not show any physical changes (color change, friability and hardness), assay and dissolution characteristics during the study period.

Study of drug release kinetics mechanism of drug release from hydrophilic Matrices

The kinetic treatment reflected that release data of selected formula F8 showed r^2 value of 0.991which is close to 1, indicating that release of drug follows zero order kinetics. The in vitro drug release of F4 was best explained by Higuchi's equation, as the plots showed the highest linearity (r^2 =0.9534). The drug release significantly follows a zero order kinetic model for formulation F8. As the plot showed the highest linearity (r^2 = 0.9891). The slope values of selected formulations (F8) for Korsemeyer and Peppa's diffusion model was >1 (0.6168) and exhibited as release mechanism of drug through polymeric membrane was found through diffusion and rate of diffusion is controlled by swelling of polymer.

Table 1: Result of study of physical parameters of Aceclofenac and formulations F1-F8

Material	Angle of repose (Degree)	Bulk density (gm/ml)	Tapped density (gm/ml)	Compressibility Index	Hausner ratio
Aceclofenac	32.92°	0.652	0.833	21.73	1.270
F1	27.23°	0.596	0.748	18.45	1.289
F2	26.46°	0.601	0.740	18.98	1.356
F3	28.36°	0.623	0.736	17.95	1.245
F4	29.21°	0.589	0.725	18.65	1.198
F5	29.56°	0.623	0.745	18.24	1.244
F6	25.62°	0.611	0.712	19.65	1.301
F7	27.35°	0.609	0.765	18.11	1.321
F8	28.76°	0.612	0.750	18.36	1.225

Table 2: Various formulations of Aceclofenac sustained release tablets

Ingredients	Wet granulation mg / tablet							
	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	200	200	200	200	200	200	200	200
Lactose	75	43	40	40	25	25	25	30
Mannitol	-	-	-	25	25	25	25	30
HPMC K100	-	-	32	70	110	66	46	36
HPMC K15	30	58	23	28	-	-	-	-
Povidone	8	7	7	8	8	9	9	9
Isopropyl alcohol	90	80	80	80	80	90	110	110
Aerosil	3	3	3	-	-	-	-	-
Talc	7	7	7	7	7	6	6	6
Magnesium stearate	7	7	7	7	9	9	9	9
Average weight	320	325	319	385	384	340	320	320

Table 3: Evaluation of uncoated sustained release matrix tablets

Formulations	Weight variation (in mg)	Thickness (in mm)	Diameter in (mm)	Hardness (in Kg/cm^2)	Friability (%)
F_1	320	3.95	9.58	6.2	0.62
F_2	325	3.98	9.58	6.4	0.53
F_3	319	3.60	9.57	6.8	0.71
F_4	386	6.00	9.58	6.0	0.54
F_5	384	4.70	9.58	5.0	0.78
F_6	340	4.15	9.57	5.5	0.53
F_7	320	3.97	9.58	4.6	0.53
F_8	320	3.95	9.58	5.4	0.51

Table 4: Data for dissolution profiles of various formulations F1-F8

Label claim 200 mg	Percentage cumulative drug release from various formulations							
Time in hours.	F1	F2	F3	F4	F5	F6	F7	F8
2nd	5.06	4.07	2.62	3.58	2.05	1.14	2.06	2.63
4th	102	2.34	9.85	25.21	26.05	33.07	51.60	33.41
6th	-	70.52	26.77	37.35	33.52	40.63	60.42	40.54
8th	-	82.65	35.23	44.82	48.45	51.54	68.63	46.00
10th	-	95.15	42.85	53.42	56.74	60.09	75.02	54.10
12th	-	-	51.10	60.94	64.86	69.65	83.14	66.06
16th	-	-	61.98	71.26	73.29	78.33	90.18	75.28
20th	-	-	74.65	79.88	81.87	86.84	97.02	88.95
24th	-	-	86.47	87.44	90.65	93.21	-	95.72

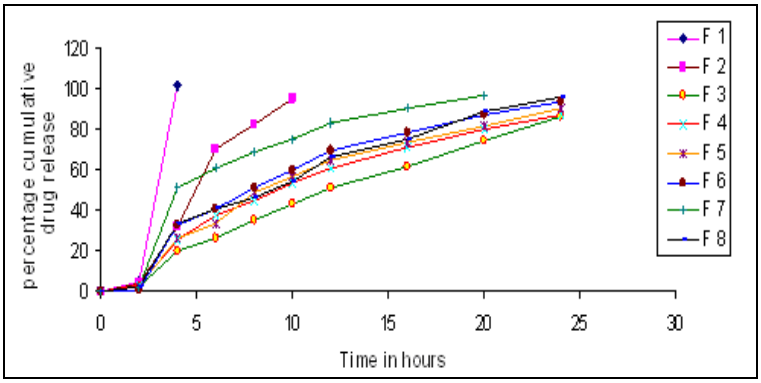

Fig. 1: Comparative dissolution profiles for various formulations F1-F8

CONCLUSION

The study was undertaken with the aim to Formulation and evaluation of Aceclofenac sustained release tablet using HPMC grade of polymer as retarding agent.

From the above results and discussion, it is concluded that the formulation of sustained release tablet of Aceclofenac containing HPMC K100, Mannitol and Lactose which are taken as ideal or optimized formulation of sustained release tablet for 24 hours release as it fulfills all the requirement of sustained release tablet and study encourages further clinical trials and long term stability study on this formulation.

REFERENCES

1. Tripathi.K.D, Essentials of medical pharmacology, 6th Edition, 2009, J.P. Publication 184-195.
2. Goodrich BF. Controlled Release Tablets and Capsules. Bulletin no. 17, Brecksville OH. Ed 1995.
3. Chien Y. W., Regulatory considerations in controlled release medication, Novel Drug
4. Delivery Systems, Marcel Dekker, New York, 1982,.577-578.
5. Remington, The science and practice of pharmacy, 20th Edition, vol -1, 1995. ISE publication 303, 907-910.
6. Leon lachman.Hobert A Liberman, Joseph L Kanig. The theory and practice of industrial pharmacy. 3rd edition (Indian).1987. Varghese publishing House 180-192.
7. Indian pharmacopoeia 2007, 5th edition. 681.
8. Gilberts, Banker. Modern pharmaceutics, 2nd edition, 1990, 647-649.
9. A.S.Tataratil J.Kouz. Investigation into the mechanisam of release and formulation, development of sustained release matrix tablets of an antiallergenic, sch-x. International journal of pharmaceutical science, 2007 234-237.
10. Dr.Umesh.d.shivhare,Nandikishore.D.Adhao,Dr.Kishore.P.Bhus ari, Dr.Vijay.B Muthr, Mr.Digvijay.U.Ambulkar "Formulation development, evaluation and validation of sustained release tablets of Aceclofenac"; International Journal of Pharmacy and Pharmaceutical Sciences, Vol. 1, Issue 2, Oct-Dec. 2009.
11. Indranil Kumar Yadav, Hari prathab singh,rana prathab singh,pan kumar thivari, Dinesh Chandra, Durg jaiswall, and D.A Jain. "Formulation, evaluation and optimization of Aceclofenac sustained release matrix tablets", International Journal of PharmTech Research. Vol.2, No.1, 592-598, Jan-Mar 2010.
12. Lee P.I. Diffusional release of a solution from a polymerize matrix approximate analytical solution, Journal of membrane science, 1980, 7, 225-275.
13. Shrinivas mutalik, Krishanan manoj, Meka sreenivas and Pralhad kusthagi. AAPS Pharma tech, Vol-9, no: 2, June 2008, 651-657.
14. Teja soni, Chira nagda, taja Gandhi, and N.P chotai. Develepoment of discriminating method for dissolution of Aceclofenac marketed formulation. Dissolution technologies 2008, 31-38.