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Development Of Prolong Release Core Tablet Formulation By Polymeric Embedding.

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ABSTRACT

The prolong release dosage form fabrication requires use of polymers for sustaining the release. During last 25 years, many coating materials are introduced for prolong release dosage form. The incorporation of drugs into polymer matrices is considered a valid tool to optimize insufficient features of the drug molecule, like solubility, stability or toxic effects. Work aimed to formulate prolong release drug delivery system of aceclofenac having short half-life by polymeric embedding in HPMC K100 M. In the present work, the incorporation of aceclofenac was performed in inert HPMC. HPMC polymer is used in different concentrations to achieve prolong release kinetics for the drug. There was no chemical interaction between the drug and polymers, confirmed by IR. Angle of repose, percent compressibility and bulk density studies reveal good flow property of granules prepared with polymers. From the dissolution studies, it was observed that all batches gave the release by diffusion-dissolution controlled mechanism. The dispersion of the drug in the polymer network altered its dissolution profile at pH 6.8, thus making it possible to obtain a gradual and prolong release, and to modulate the release pattern.

Keywords: Aceclofenac, HPMC K 100M, tablet.

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INTRODUCTION

Development cost for new drug molecule is very high. The primary objectives of prolong release drug delivery are to ensure safety and enhancement of efficacy of drug with improved patient compliance. So, the use of such delivery is increasing in treatment of acute and chronic diseases as they maintain the concentration of drug in plasma above minimum effective concentration and below the minimum toxic level for extended period of time. Thus, prolong release drug delivery results in optimum drug therapy with reduced frequency of dosing and side effects [1]. A tablet is a mixture of API and excipient usually in powder form, pressed or compacted in to solid. The excipients usually include binders, lubricants, glidents, disintegrants, sweeteners or flavours and pigments [2]. Prolong release tablet allowing a two-fold or greater reduction in frequency of administration of a drug in comparison with the frequency required by a conventional dosage form [3]. Particles of drug are coated with matrix or entire product is matrix coated which along with its main function of prolong action, avoid exposure of unstable drug to the environment and render it stable [4].

Prolong release of drug can be achieved by [5]

Dissolution controlled release system

Embedding the drug in slowly dissolving or erodible matrix (monolith)

In this system, the drug is homogeneously dispersed throughout a rate controlling medium and employs waxes such as bees wax, carnauba wax, hydrogenated castor oil etc. Dissolution of drug is controlled by controlling the rate of penetration of dissolution fluid into the matrix by altering the porosity of tablet, decreasing its wet ability or by itself getting dissolved at slower rate. The drug release is often followed by first order kinetics from such matrices. A major disadvantage of matrix system is that drug release rate continuously decreases with time due to increased diffusional distance and decreased surface area at the penetrating solvent front.

Consequently, to achieve zero order release, it is necessary to select geometry that compensates the increase in diffusional distance with the corresponding increase in surface areas for the dissolution. To achieve zero order drug, release a novel approach is proposed by incorporating nonuniform drug distribution in a matrix material.

Encapsulation or coating with slowly dissolving or erodible substances (Reservoir devices)

These systems generally employ coating of drug particles or granules with slowly dissolving materials. The coated particles can be directly compressed into tablets like a spacetabs or placed in a capsule as in the spansule products. Time required for the dissolution of the coat is a function of thickness of coat and its aqueous solubility. One can obtain controlled action by employing a wide spectrum of coated particles of varying coat thickness. Coating can be achieved by one of the several micro encapsulation techniques with slowly dissolving materials like cellulose.

Diffusion controlled release system

Matrix diffusion controlled systems

In these systems, the dug is dispersed in an insoluble matrix of rigid non-swellable hydrophobic materials or swellable hydrophilic substances. For rigid matrix, insoluble plastics such as PVC and fatty materials like bees wax, stearic acid etc. are used. While for the swellable matrix hydrophilic gums of natural origin (tragacanth, guar gum), semi synthetic (HPMC, Xanthan gums, CMC), or synthetic (polyacrylamides) can be used.

Reservoir Devices:

In these systems, an inner core of drug is surrounded by a water insoluble polymeric membrane. The polymer can be applied by coating or microencapsulation techniques. Commonly used polymers are HPC, Ethyl

cellulose and polyvinyl acetate. The drug release mechanism across the membrane involves its partitioning into the membrane with subsequent release into the surrounding fluid by diffusion.

Dissolution and Diffusion controlled Release system

In such system, the drug core is enclosed in partially soluble coating. Pores are formed due to dissolution of parts of the membrane which can permit entry of dissolution fluid into the core and hence drug dissolution and allow diffusion of dissolved drug out of the system.

Objective of present work

The oral administration of drug for acute as well as chronic disease management is the convenient, safe and effective means of delivery. NSAID's, antihypertensive, anti-ulcer agents are administered orally in prolong release dosage forms for management of chronic diseases.

Drugs having short half life, needs frequent dosing thus, there may be accumulation which leads to toxicity and thus cause patient inconveniences. All these need a properly designed prolong release dosage formulation which also minimizes the fluctuations in blood concentration and risk of side effects. The prolong release dosage form fabrication requires use of polymers for sustaining the release. During last 25 years, many coating materials are introduced for prolong release dosage form.

Work aimed to formulate prolong release drug delivery system of aceclofenac having short half-life by embedding it in HPMC K100 M to formulate matrix. Then the formulated core tablets were evaluated for its physicochemical properties and invitro release studies include its invitro release kinetics.

MATERIAL AND METHOD

Materials

Aceclofenac was obtained as a gift sample Suyesh Lab, India. HPMC K100M was obtained as gift sample from Colorcon Asia Pvt. Ltd. (Goa, India). All other chemicals and reagents were of analytical grade.

Calibration Curve of aceclofenac in Phosphate Buffer pH 6.8 [6]

Weight accurately about 100 mg of aceclofenac working standard in a 100 ml volumetric flask add sufficient dissolution media, Sonicate to dissolve and make up the volume with dissolution media and mix. Dilute 1 ml of this solution to 100 ml with 6.8 phosphate buffer. Filter the solution through Whatman No.42 filter paper. Absorbance values of this solutions were measured 275 nm using Shimadzu UV/Visible spectrophotometer (Fig. 1 and 2).

Method of preparation of core tablets by polymeric embedding [7]

Tablets were prepared by wet granulation method. In which PVP was dissolved in sufficient water. Aceclofenac, DCP, and MCC were taken into plantery mixer and mixed well then PVP solution was added to it and damp mass was prepared. This was dried in dryer 30 min at 50^0C temp. After drying shifted through sieve 20# and granules were prepared. HPMC K100M, talc, aerosol and magnesium stearate were mixed in granules. After granule preparation, 500 mg of granules equivalent to 200 mg of aceclofenac were weighted and tablets were compressed on 16 station tablet compression machine (Rimek). Using 10 mm punch size. Different batches of granules F1 to F6 were prepared by using different polymer concentration (Table 1) and tablets were compressed and evaluated for the drug release.

Compatibility studies

Drug polymer compatibility study was done by IR. The IR spectrum of aceclofenac and physical mixture of drug and polymers were recorded using JASCO FTIR-5300. The pellets were prepared in KBr press using physical mixture of drug, polymers and KBr. The spectra were recorded over the scanning range of 4000-400cm^{-1} (Fig. 3 and Table 2).

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Evaluation of granules [8]

Angle of repose

Angle of repose was determined by Neumann's method and calculated using the formula, for unlubricated as well as lubricated granules.

$\tan \theta = h/r$

$\theta = \tan^{-1} (h/r)$ Where, h = height of pile, r = radius of the pile base

Bulk density

The bulk density was calculated using equation,

$$\rho b = M/V$$

Where, ρb = Bulk density
M = Mass of the granules ingrams
V = Final untapped volume of granules in ml.

True density

The true density was calculated using equation,

$$\rho t = M/Vp$$

Where, ρt = true density
M= Mass of granules in grams
Vp= Final tapped volume of granules in ml.

Hausners ratio

Hausners ratio was calculated as follow

$$\text{Hausner ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Compressibility index

Compressibility index of the powder was determined by

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

Loss on Drying (LOD)

The moisture content of the lubricated granules was analyzed by using IR Moisture Analyzer. 5.0 gm or more quantity of granules was heated at 105^0C until the change in the weight was no more observed by the instrument. The % loss in weight was recorded.

Evaluation of Tablets [8, 9, 10]

Content uniformity

Three tablets of each type of formulation were weighed and crushed in mortar and was dissolved in 100 ml water. This was the stock solution from which l ml sample was withdrawn and diluted to 100 ml with 0.1N HCl. The absorbance was measured at wavelength 280 nm using double beam UV-Visible spectrophotometer.

Weight variation

Twenty tablets were selected randomly and weighed. Average weight of the tablet was determined. These tablets were weighed individually and the weight variation was determined.

Tablet hardness

The resistance of tablets to shipping or breakage, under conditions of storage, transportation and handling before usages are depends on its hardness. The hardness of tablet of each formulation was checked by using hardness tester. The hardness was measured in terms Newton.

Thickness

Thickness of tablet is important for uniformity of tablet size. Thickness was measured using Vernier Calipers. It was determined by checking ten tablets from each formulation.

Dissolution studies

Tablets of each formulation were subjected to dissolution rate studies. In-vitro dissolution studies were carried out to determine the drug release from various formulations. The release characteristic studies included the amount of drug released per hour up to 12 hours.

Assay [11]

Standard Preparation

Weight accurately about 100 mg of aceclofenac working standard solution in a 100 ml volumetric flask. Add sufficient methanol, sonicate to dissolve and make up the volume with 6.8 phosphate buffer and mix. Dilute 1 ml of this solution to 100 ml with 6.8 phosphate buffer and filter the solution through Whatman No.42 filter.

Sample Preparation

Weigh accurately equivalent to 200 mg aceclofenac from the mixed content of 10 crushed tablets into a 100 ml volumetric flask. Add sufficient methanol, sonicated to dissolve and make the volume to 100 ml with 6.8 phosphate buffer and mix. Centrifuge the solution for 5 minutes and filter the solution through Whatman No.42 filter. Further dilute 1 ml of the filtrate to 100 ml with 6.8 phosphate buffer.

$$\text{Labeled Amount} = \frac{\text{Content of Aceclofenac (mg/tablet)}}{\text{Label Claim (in mg)}} \times 100$$

Stability Studies [12]

An accelerated stability study was conducted for the best batch F6 for a period of two months in 40°C ± 2°C / 75 % RH ± 5 % RH. Then the tablets at specific intervals were evaluated for drug content.

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RESULT AND DISCUSSION

Compatibility study

The aceclofenac showed the characteristic peaks, shown in Table 2. From the result, it was observed that the drug and polymer were compatible with each other (Fig. 4).

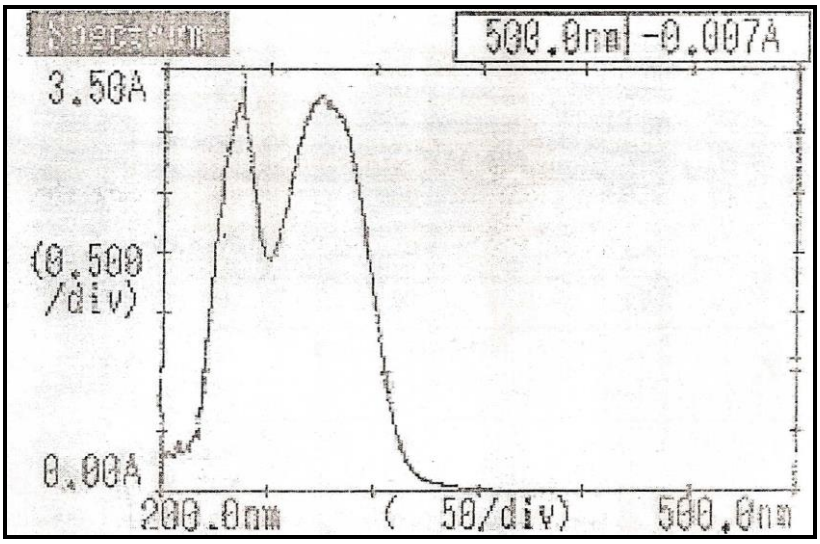

Fig 1: Spectrum of Aceclofenac in phosphate buffer of pH 6.8

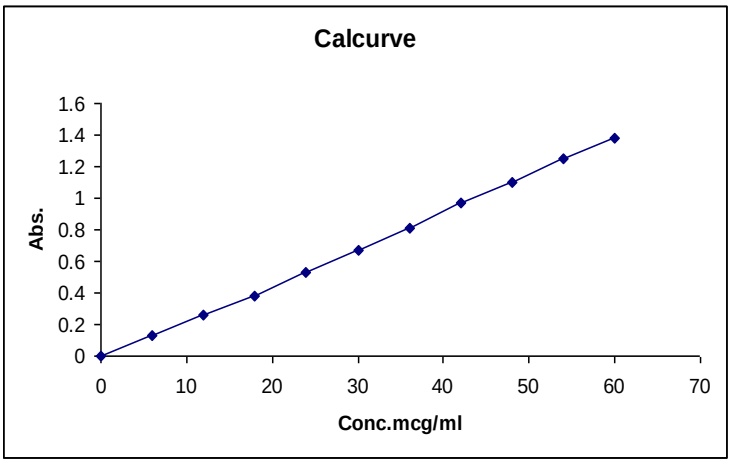

Fig 2: Calibration curve of Aceclofenac in phosphate buffer of pH 6.8

Table 1: Formulations with different conc. of HPMC K100M

Ingredients	F1	F2	F3	F4	F5	F6
Aceclofenac(mg)	200	200	200	200	200	200
Microcrystalline cellulose (mg)	40	45	50	55	60	65
Dicalcium phosphate	35	35	35	35	35	35
PVP k 30	15	15	15	15	15	15
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Polymeric Embedding						
HPMC K100M (mg)	55	50	45	40	35	30

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Talc	1.5	1.5	1.5	1.5	1.5	1.5
Aerosil (mg)	1.0	1.0	1.0	1.0	1.0	1.0
Magnesium stearate (mg)	2.5	2.5	2.5	2.5	2.5	2.5

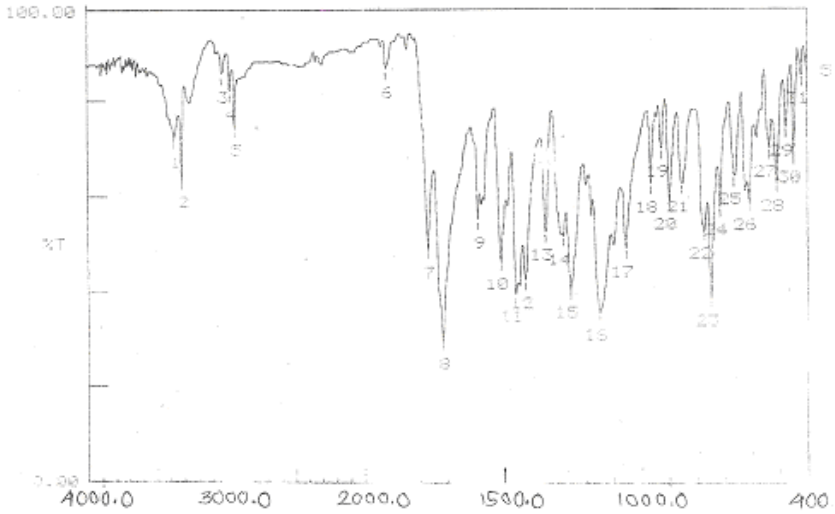

Fig 3: IR of Aceclofenac peak

Table 2: IR data of Aceclofenac

Functional groups	**Absorption cm^{-1}**
C=0 stretching	1770.81 1716.80
OH stretching	2970.64
CH stretching superimposed on OH stretching	2937.85
NH stretching	3319
C-Cl	669.50

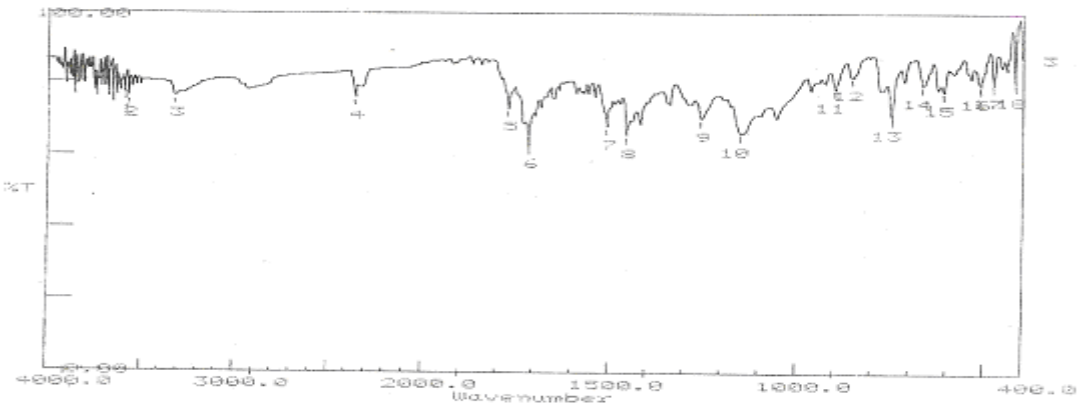

Fig 4: IR spectrum of Aceclofenac+HPMCK100M

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Powder and Granule Properties

Powder and granules properties were within the standard and showed good packing capacity (Table 3).

Table 3: Powder Properties of Formulations F1 – F6 before addition of glidant and lubricant

Sr. No.	Granule properties	Formulations					
		F1	F2	F3	F4	F5	F6
1	Angle of repose	30.1	28.44	29.47	26.56	26.13	27.47
2	Flow rate (gm/sec.)	0.903	0.91	0.89	0.91	0.93	0.916
3	Bulk Density (gm/cc)	0.3872	0.39	0.3854	0.386	0.395	0.381
4	Bulkiness	2.582	2.56	2.59	2.59	2.531	2.624
5	Loose Bulk Density	0.3388	0.341	0.337	0.334	0.342	0.335
6	Void Volume(cc)	1.0	1.0	1.0	1.1	1.1	1.0
7	Porosity (%)	12.5	12.5	12.5	13.42	13.42	12.2
8	% compressibility	12.5	12.57	12.5	13.48	13.42	12.08

Tablet Properties

Tablets were prepared by wet granulation (F1 – F6). All the formulations were evaluated for various parameters. Observations are shown in Table 4. The % deviation in weights of tablets was $\pm$ 10 % which is within the range according to IP. This shows uniform die fill during tablet compression. The tablets were analyzed for potency. The drug content uniformity was in range of 95-99% showing uniform distribution of drug in matrix. As there was no much variation in thickness of tablets in each formulation, it shows that granules and powder blends were consistent in particle size and uniform behavior during compression process. The hardness of tablet was measured on Erweka hardness tester. The hardness was in range of 8-14 kg/cm^2. The two factors i.e. high value of hardness and absence of disintegrant in formulation, indicate that tablet will not disintegrate in gastrointestinal tract and release the drug slowly by diffusion process. Friability was found to be 0.2 – 0.6 %. As friability was below 0.8 % tablets in each formulation can withstand the mechanical shocks.

Table 4: Tablet Properties of core tablet

Formulation	Average weight (mg)	Diameter	Thickness (mm)	Hardness (kg/cm^2)	% Friability
F1	**350**	**10.21**	**4.53**	**10.2**	**0.0054**
F2	**355**	**10.23**	**4.56**	**9.2**	**0.023**
F3	**354**	**10.21**	**4.45**	**9.8**	**0.025**
F4	**358**	**10.19**	**4.63**	**9.8**	**0.0042**
F5	**352**	**10.21**	**4.52**	**10.5**	**0.044**
F6	**351**	**10.17**	**4.64**	**11.8**	**0.028**

Invitro release studies

All the formulations were subjected to dissolution studies and it was observed that the batch F6 showed about 99.89% of release and it was the highest release when compared to other batches. The batch F1 and F2 showed a very slow release with about only 21.77% of release at the end of 12hrs whereas, batches F3, F4 and F5 gave a release about 66 to 89% of release. (Table 5 and Fig. 5)

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Table 5: In-vitro release profile for different batches

Time (Hrs)	Formulations (% Drug Release)					
	F1	F2	F3	F4	F5	F6
1	4.40	11.20	15.76	19.55	26.21	28.30
2	6.65	16.84	21.65	28.55	31.61	34.10
3	8.32	19.32	28.88	32.45	35.87	39.90
4	9.65	22.32	35.12	37.22	41.22	47.20
6	11.76	26.09	45.26	44.21	52.54	57.60
8	15.32	29.43	53.28	58.32	63.55	75.40
10	18.95	32.10	60.33	63.19	72.66	83.00
12	21.77	36.43	66.32	78.09	89.44	99.82

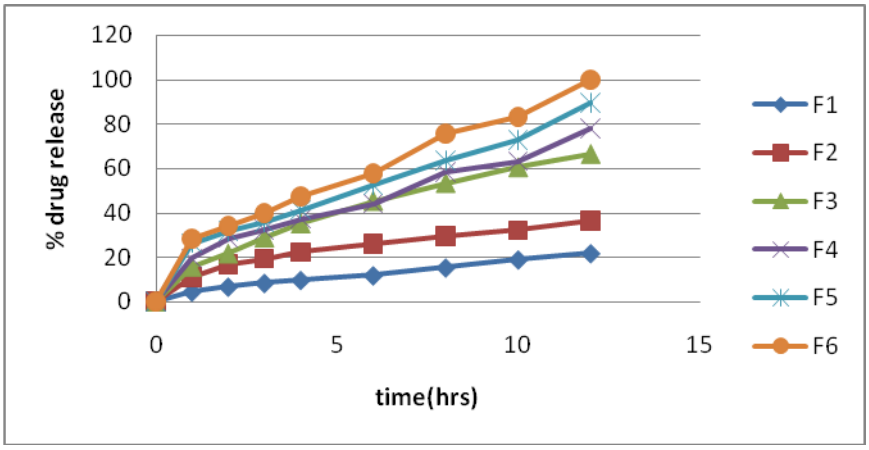

Fig 5: In- Vitro drug release

In vitro % drug release F6 Formulation in comparison to marketed formulation

The selected best F6 batch was compared with a marketed product for invitro release. It was found that our formulated product matched with marketed product effect. (Table 6)

Table 6: %drug release comparison between optimized and market sample

Time(Hrs)	Optimize Formulations (% Drug Release)	Marketed Formulations (% Drug Release)
1	28.30	29.50
2	34.10	35.50
3	39.40	46.40
4	47.40	51.10
6	57.60	58.90
8	75.40	79.40
10	83	92.40
12	99.82	99.54

Assay

Aceclofenac are fond to be freely soluble in 6.8 phosphate buffer, the media use for determination of aceclofenac determination by UV absorbance spectroscopy is 6.8 phosphate buffer solutions. The scanning graph of aceclofenac in media is shown in the Fig. 6. Drug content was shown in Table 7.

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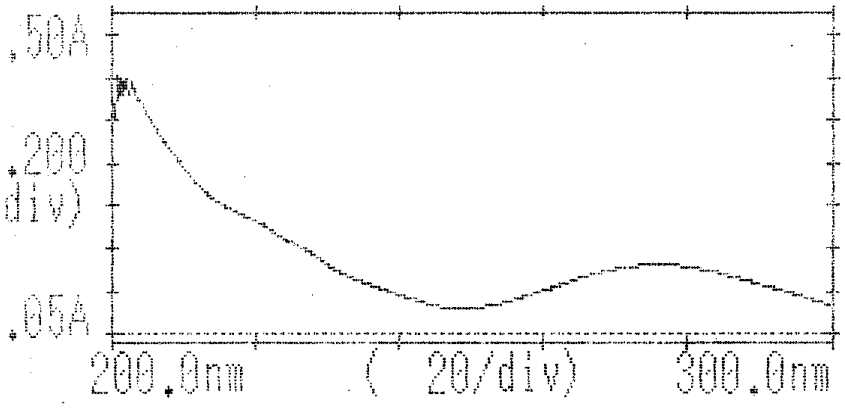

Fig 6: Scanning graph of Aceclofenac by UV

Table 7: Aceclofenac drug content

Sr no	Batch no	Drug content
1	F1	99.56
2	F2	98.45
3	F3	99.12
4	F4	98.22
5	F5	97.44
6	F6	99.61

Stability studies

The packed formulations were stored in stability chambers maintained at 40°C and 75% relative humidity for one month. From the results obtained it was observed that the drug loss on storage was found to be normal (Table 8).

Table 8: Accelerated stability study protocol

Condition	40°C/75%RH		
Batch No.	F6		
Test	Initial	1 Month	2 month
Time (Hour)	0	0	0
1	28.30	27.54	26.74
2	34.10	33.74	33.76
3	39.40	39.50	40.54
4	47.40	45.12	44.32
6	57.60	53.92	62.02
8	75.40	73.64	72.86
10	83	81.76	83.65
12	99.82	98.23	97.66
Assay	99.10	99.04	98.76

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CONCLUSION

In the present work, the incorporation of aceclofenac was successfully attempted in inert HPMC. The incorporation of drug into polymer matrices is considered a valid tool to optimize insufficient features of the drug molecule, like solubility, stability or toxic effects. HPMC polymer is used in different concentrations to achieve prolong release kinetics for the drug. There was no chemical interaction between the drug and polymers, confirmed from IR.

Angle of repose, percent compressibility and bulk density studies reveal good flow property of granules. Tablets prepared by wet granulation have passed the evaluation tests for tablets as per Indian Pharmacopoeia 1996.

From the dissolution studies, it was observed that all batches gave the release by diffusion-dissolution controlled mechanism. The dispersion of the drug in the polymer network altered its dissolution profile at pH 6.8, thus making it possible to obtain a gradual and prolong release, and to modulate the release pattern. Optimized batches show similarity characteristics with market product.

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