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FORMULATION AND EVALUATION OF ACECLOFENAC SODIUM BILAYER SUSTAINED RELEASE TABLETS

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ABSTRACT: The objective of the present research was to develop a bilayer tablet of Aceclofenac sodium using superdisintegrant, sodium starch glycolate for the fast release layer and water immiscible polymers such as Eudragit RL100 for the sustaining layer. Tablets were evaluated for Physico-Chemical properties such as Hardness, Friability, Thickness, Weight Variation and Drug content uniformity. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. *In Vitro* dissolution studies were carried out in a USP type II Paddle type apparatus. The formulation gave an initial burst effect and followed by sustained release for 24 hrs. The optimized formulation (F5) showed no significant changes on stability studies when storing at 4º c, 40º c, /75%RH, 60º c/80% RH for 3 months. The TG /DTA analysis revealed that there was no significant interaction between polymers and drug .The drug release from F5 Formulation was found to zero order kinetics. It was also found linear in Higuchi's plot which confirms that diffusion is one of the mechanism of drug release .In this study optimized formulation (F5) release the drug upto 24hrs and fulfilled many requirements such as easy to fabricate , cost effective and high patient compliance.
Keywords: Aceclofenac sodium, bilayer tablets, sodium starch glycolate, sustained release, Eudragit RL100, croscarmellose, lactose.

INTRODUCTION

Aceclofenac sodium is an Non Steroidal Anti inflammatory COX-2 Inhibitor. It is widely used in osteoarthritis, Rheumatoid arthritis, Ankolysing spondylitis. [1, 2]. Physico-Chemical properties, Biological properties of Aceclofenac help us to making formulation of sustained release easily. The plasma half life of aceclofenac is 3-4 hours. [3]. . So it is suitable candidate for sustained release. Eudragit RL100 is one of the sustained release polymer which gives the release upto 24hrs. Amount of drug polymer used was 20% calculated on drug respectively. Eudragit RL100 available in granules. Methacrylate copolymers with tri methyl ammonia ethyl methacrylate as a functional group. Eudragit RL100 properties are insoluble, high permeability, P^H independent, swelling. Benefits of Eudragit RL100 are time-controlled release of active ingredient therapeutically [4]. The multilayered tablet concept has been long utilized to develop sustained release formulation such a tablet has a fast releasing layer and may contain bi or triple layer to sustain the drug release [5]. The pharmacokinetic advantage relies on the fact that the drug release from fast releasing granules leads to sudden rise in blood concentration. However blood level is maintained at steady state on the drug is released from sustained granules. Several mathematical models have been published to elucidate the water and drug transport processes and to predict the drug release

MATERIALS

Aceclofenac sodium was obtained from a gift sample, (Madras Pharmaceuticals, Chennai). sodium starch glycollate (Himedia Labs, Mumbai) ,Eudragit RL100 (Matrix Pharmaceuticals, Mumbai), talc and magnesium stearate was obtained from (Swastika Pharmaceuticals, Chennai). starch was procured from (Meghana Products, Chennai).

Preformulation studies :

The parameters like identification of pure drug Aceclofenac sodium by IR spectra (Fig.1) , drug excipients compatability studies , angle of repose, bulk density , tapped density , Hausner ratio, carr's index [6 ,7] and loss on drying were evaluated.

Compatibility study:

Aceclofenac sodium granules with various excipients in glass vials were taken and kept at various accelerated condition (30˚c/ 65% RH, 40˚ c / 75%RH and 60˚ c / 80%RH) in stability chamber
(Osworld stability chamber, India) for three months in open and closed condition. The sample were withdrawn on 1st, 2nd , 3rd 4th ,5th 6th,7th 14th 21st and 30th day and physical characteristics like colour change if any was recorded . Finally the mixtures with no colour change were selected for formulations [8].

Preparation and characterization of Bilayer Tablets

The bilayer tablets of Aceclofenac sodium were prepared by direct compression method. The drug and polymers for both fast release and sustaining layer were passed through a 180 µm seize before their use in the formulation.

Formulation of the Fast Release Layer [9]

The dose in the formulation for fast release was 70mg, the maintenance dose or sustained dose 130 mg of Aceclofenac sodium was calculated as per modified release tablets limit given in U.S.P [10] The fast release granules were prepared by direct compression technique by blending Aceclofenac sodium uniformly with sodium starch glycolate and croscarmellose given in table I. The granules were mixed with talc and magnesium stearate.

Formulation of the Sustained Release Layer ([11])

Sustaining granules were also formulated by direct compression technique by mixing Aceclofenac sodium uniformly with Eudragit RL100 and lactose was given in Table 2. The sustaining granules were also, subjected to similar processing steps on the fast releasing granules.

Characterisation of Granules

Prior to compression, granules were evaluated for their characterestic parameter such as tapped density, Carr's Index and angle of repose. Carr's compressibility index was calculated from the bulk and tapped density using a digital tap density apparatus (Electrolab India).

Compression of Bilayer Tablet [12]

The quantity of granules for the sustained release layer was compressed lightly using a single punch tableting machine (Cadmach machinery Co., Pvt., Ltd) equipped with 9 mm round flat and plain punches. Over this compressed layer the required quantity of the fast release layer was placed and compressed to obtain hardness in the range of 5 – 6 kg/cm^2 to form a bilayer matrix.

Physical test for Bilayer Tablets

Standard physical test for the bilayer matrix tablets were performed and average values were calculated. Mass variation was determined by weighing 20 tablets individually. Hardness was determined by taking 6 tablets from each formulation using a Monsanto hardness tester (Royal scientific Pvt., Ltd.Chennai,).The values were given in Table .3

DRUG CONTENT UNIFORMITY:

Ten tablets were finely powdered and an amount equivalent to 100 mg weighed & transferred to100 ml volumetric flask and 70 ml of methanol was added. The flask was shaked for 10 min. Finally the volume was made up to mark with methanol. Then it was analyzed in U.V. Spectrophotometer. (Elico Ind, Ltd., India) at 275nm [13].

DISSOLUTON TEST

Invitro drug release was performed using dissolution apparatus USP type II paddle method (TDT – 08L, Ellector lab, India) with a stirring speed of 50 rev/min at 37 ˚c ± 0.5 in 0.1 Hcl for 2 hours and 900ml of 7.5 phosphate buffer for 24 hours. The samples were taken at pre selected time intervals with replacement of equal volume of dissolution media the collected samples were diluted & the absorbance was measured spectrophotometrically at 275nm. (UV – visible spectrophotometer 1601, Shimadzu corporation, Japan) (USP, 2006) [14]

STABILITY STUDIES

The tablets were packed and kept for 3months at 4˚ c in refrigerator, 40 ˚ c / 75% RH in a stability chamber (Oswald, Mumbai) 60 ˚c/ 80% in incubator. At the interval of 15 days tablets were withdrawn and evaluated for physical properties like thickness, hardness, diameter, friability, weight variation and content uniformity, *Invitro* drug release and assay were also carried out [15]

TG / DTA STUDIES

For optimized formulation F5 (Aceclofenac sodium: eudragit RL 100 130:65) thermogravimetry / differential thermal analysis were performed to characterize drug excipients compatibility. The TG / DTA thermo grams of pure drug and mixture recorded in a TG /DTA analyzer (SDT Q 600, India) at a heating rate of 20 ºc / min from 30 to 400˚ c in a nitrogen atmosphere.

MECHANISM OF DRUG RELEASE

Korsemeyer desired a simple relationship which described drug release from a polymeric system equation to find out the mechanism of drug release, the drug release data was fitted in Korsemeyer –Peppas model.

$Mty / M\alpha = Kt$

Mt/Mά is the fraction of drug released at time't' K is the rate constant and n is the release exponent. [16]

RESULT & DISCUSSION

The prepared bilayer tablets were evaluated for various physical properties. The bulk density for the granules of various formulations ranged between 0.87 $\pm$ 0.14 and 2.42 $\pm$ 0.42 gmL^{-1} as determined by the tap

method. This value of bulk density indicates of good packing character. The compressibility Index (CI) for all formulation was found to be below 15% indicating desirable flow properties. The flow properties of granules were further analyzed by determining the angle of repose for all granules. It ranged between 21.32 ± 0.58 to 25.03 ± 0.23. The value indicates good flow property of granules with Eudragit RL 100; all the batches of tablets were produced under similar conditions to avoid processing variable. Average weight, hardness and thickness of tablets were 300mg ± 5 hardness was 5.2 kg/cm^2 ± 1.2 and thickness was 3.7 mm. ± 0.1 The percentage friability of all formulation was 0.7 ± 0.01% values of hardness test and percentage friability indicate good handling properties of the prepared bilayer tablets. The drug content uniformity in bilayer matrix tablets was 98.5% ± 0.14.

FT- IR spectrum of Aceclofenac bilayer sustained release tablets revealed there is no major interaction between drug and polymers used in the study.

The release of Aceclofenac sodium from fast releasing layer was analysed by plotting the cumulative percent drug release Vs time. It shows an initial burst effect. From all the formulation over 30% of Aceclofenac sodium was released within 2 hrs of dissolution study was showed in (Fig.2)

Eudragit RL 100 has been used as the release retardant polymer in controlled release dosage forms. Eudragit reduced the drug release due to reduction in the penetration of the solvent molecular into the system because of hydrophobic nature and Eudragit present on the surface of tablets. (i.e.). The rate of release is controlled by the permeability of matrix structure. Formulation of bilayer tablet containing Drug: Polymer ratio 1:01, 1:0.2, 1:03, 1:04 shows that it could not sustain the release beyond 12 hours.

1:0.5 showed the desired release profile over the test period for 24 hours. In this selected formulation, the calculated regression coefficient for Higuchi, Peppa's models were 0.991, 0.967 respectively. Therefore the release seems to fit the Higuchi model was showed in (Fig. 3). Higuchi's Plot, Peppas's Plot (Fig.4) states that release followed the diffusion controlled mechanism.

TABLE 1 : COMPOSITION OF FAST RELEASING LAYER

COMPOSITION	**FAST RELEASING LAYER (MG)**
Aceclofenac Sodium	70 mg
Sodium Starch Glycolate	5 mg
Croscarmellose	5 mg
Starch	18 mg
Talc	1 mg
Magnesium stearate	1 mg

TABLE 2 : COMPOSITION OF SUSTAINING LAYER (IN DIFFERENT RATIOS)

COMPOSITION	**DRUG : EUDRAGIT RL 100 RATIO**				
	(F1) 1:0.1	**(F2) 1:0.2**	**(F3) 1.0.3**	**(F4) 1:0.4**	**(F5) 1:0.5**
Aceclofenac Sodium	130mg	130 mg	130 mg	130 mg	130 mg
Endragit RL 100	13 mg	26 mg	39 mg	52 mg	65 mg
Lactose	51 mg	42 mg	29 mg	16 mg	3 mg
Talc	1 mg	1 mg	1 mg	1 mg	1 mg
Magnesium Stearate	1 mg	1 mg	1 mg	1 mg	1 mg

TABLE 3: Physical and chemical parameters of formulated Aceclofenac tablets (F5)

Weight (%) variation (mg) ± S.D n=20	**Thickness (mm) ± S.D n=20**	**Friability (%)± S.D n=10**	**Hardness (kg/cm^2) ± S.D n=6**	**Drug content (%) ± S.D n=10**
300 ± 0.5	3.7 ± 0.1	0.7 ± 0.01	5.2 ± 0.01	98.5 ± 0.14

Fig 1:IR STUDY FOR F5 FORMULATION

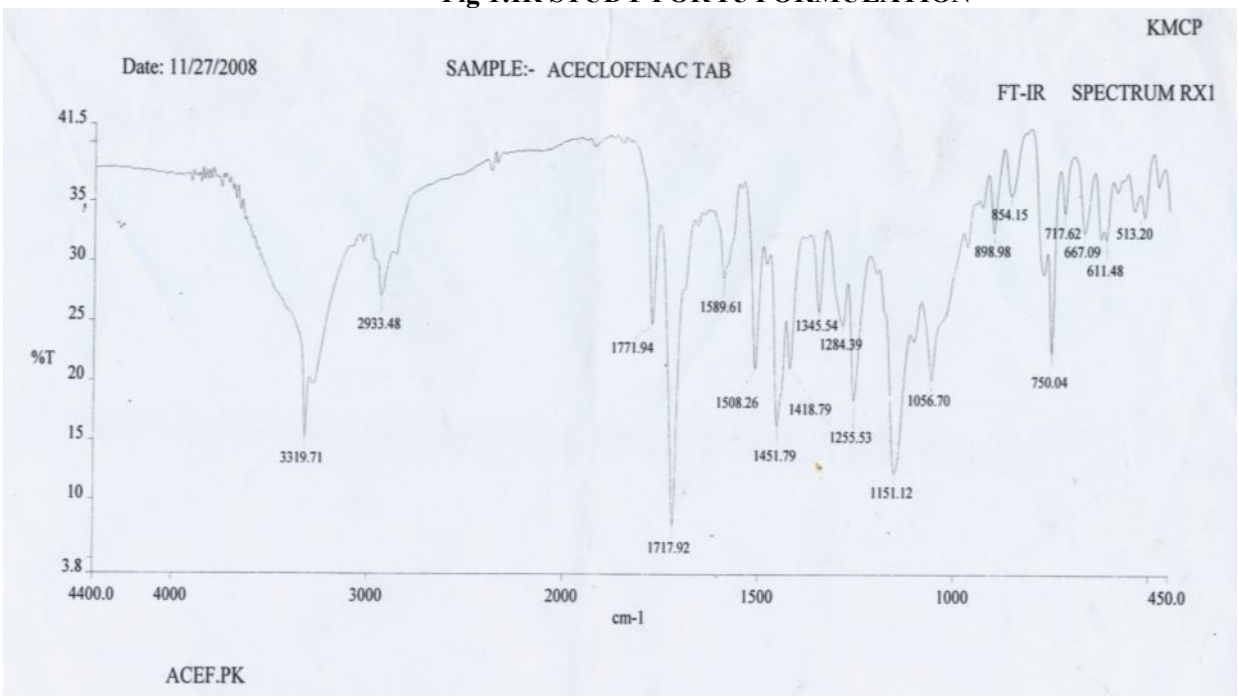


Fig 2 : INVITRO DRUG RELEASE OF F5 FORMULATION

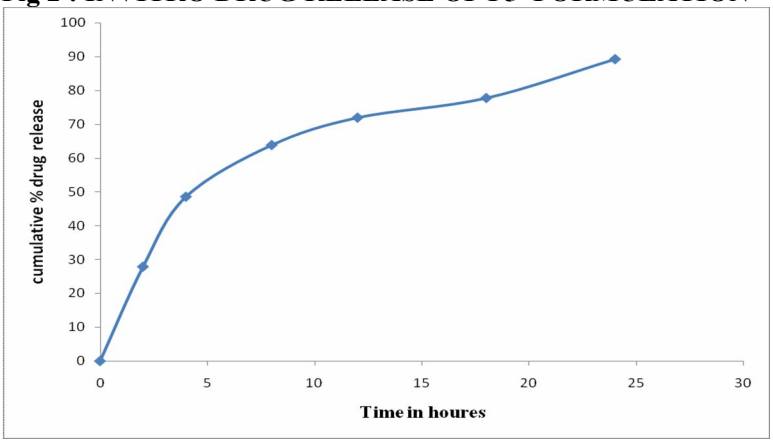


Fig 3: HIGUCHI'S PLOT FOR DRUG RELEASE (F5)

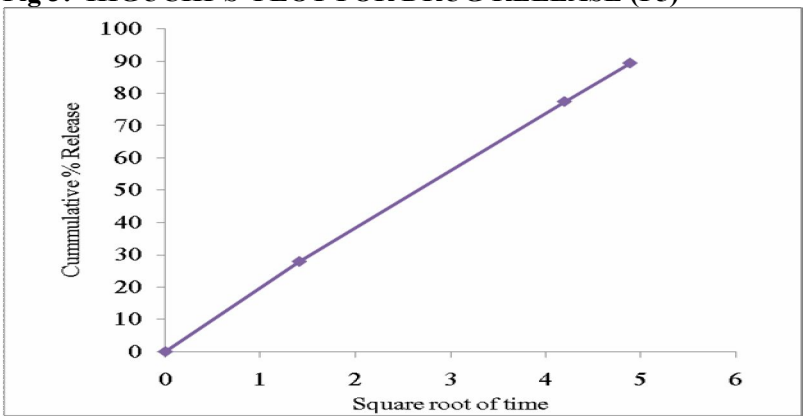
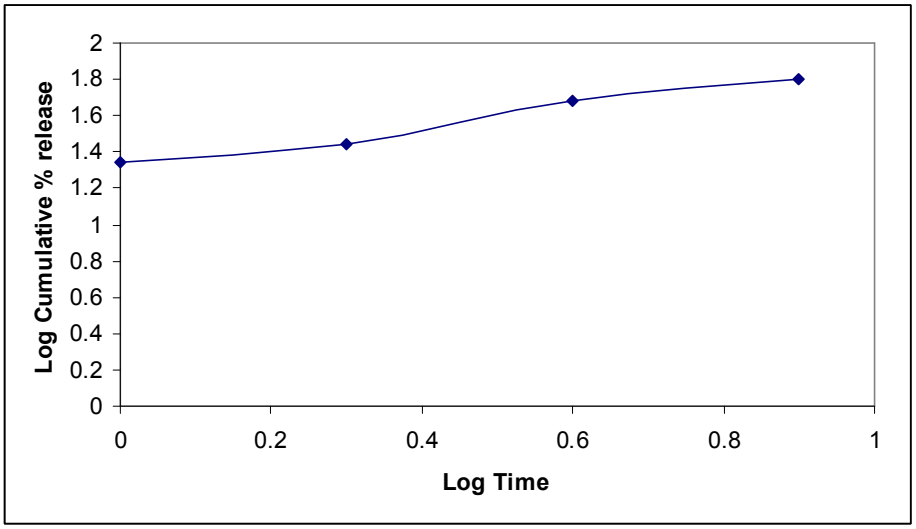


Fig 4 : KORSMEYER-PEPPAS PLOT FOR DRUG RELEASE (F5)



CONCLUSION

The present research was carried out to develop a bilayer tablet of aceclofenac sodium using super disintegrant sodium starch glycolate for fast release layer and Eudragit RL 100 for sustaining layer. Bilayer tablets showed an initial burst effect to provide the loading dose of drug, followed by sustained release for 24 hrs. This modified release bilayer tablets also reduced dosing frequency, increase the bioavailability and provide better patient compliance.

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