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FORMULATION AND *IN VITRO* EVALUATION OF SUSTAINED RELEASE MATRIX TABLETS OF ACECLOFENAC

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Abstract:

The main aim of present work was to formulate and evaluate sustain release matrix tablets of Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID). Sustain release formulation are those which delivers the drug locally or systemically at a predetermined rate for a fixed period of time. The matrix tablet was prepared by direct compression method using by various concentration of Sodium Alginate and Eudragit RLPO various release retardant polymer. The powder mixtures were subjected to various pre-compression parameters such as angle of repose, bulk density, tapped density and Carr's index shows satisfactory result and the compressed tablets are evaluated for post-compression parameters such as weight variation, thickness, hardness, friability, drug content, in-vitro dissolution studies. In-vitro dissolution studies were carried out for 12 hours using 0.1 N HCL for first 2 hours and pH 6.8 phosphate buffer for 12 hours and the result showed that formulations F5 showed good dissolution profile to control the drug release respectively. Formulation containing lower concentration of Eudragit RLPO polymer sustained the drug release for the period of 12 hours. The kinetics studies the optimized formulation followed Zero order release kinetics.

Key words: *Aceclofenac, Sodium Alginate, Eudragit RLPO, Direct compression and Sustained release matrix tablets.*

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INTRODUCTION:

Administration of drugs, which is due in part to the ease of administration and to the fact that gastrointestinal physiology offers more flexibility in dosage form design than most other routes. The terms Sustained release, prolonged release, modified release, extended release or depot formulations are used to identify drug delivery systems that are designed to achieve or extend therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. The advantages of administering a single dose of a drug that is released over an extended period of time, instead of numerous doses, have been obvious to the Pharmaceutical industry for some time. The desire to maintain a near constant or uniform blood level of a drug often translates into better patient compliance, as well as enhanced clinical efficacy of the drug for its intended use. Because of increased complication and expense involved in marketing of new drug entities, has focused greater attention on development of sustained or controlled release drug delivery systems . Matrix system is widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. The goal of an extended release dosage form is to maintain therapeutic drug level in plasma for extended period of time. [1]

Now a day's conventional dosage forms of drugs are rapidly being replaced by the new and the novel drug delivery systems. Amongst, these the controlled release/sustained release dosage forms have become extremely popular in modern therapeutics. Matrix system is the release system which prolongs and controls the release of the drug, which is dissolved or dispersed. A matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system in the field of Pharmaceutical technology. Sustained release constitutes any dosage form that provides medication over an extended time or denotes that the system is able to provide some actual therapeutic control whether this is of a temporal nature, spatial nature or both. Sustained release system generally do not attain zero order type release and usually try to mimic zero order release by providing drug in a slow first order. Repeat action tablet are an alternative method of sustained release in which multiple doses of drug are an alternative method of sustained release, in which, multiple doses are contained within a dosage form and each dose is released at a periodic interval. [2]

The goal in designing sustained or sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release (SR) dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. The goal of an SR dosage form is to maintain therapeutic blood or tissue levels of the drug for an extended period. This is usually accomplished by attempting to obtained zero-order release from the dosage form. Zero-order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system (i.e., a constant release rate). SR systems generally do not attain this type of release and usually try to mimic zero-order release by providing the drug in a slow first-order fashion (i.e., concentration dependent). [3]

Approaches of oral sustained/controlled release formulations:

To achieve the rapid action, Bolourtchian et al developed sublingual tablets of captopril which was effective and safe method of lowering arterial blood pressure in patient with hypertensive emergencies. More rapid attainment of plasma concentration and more rapid onset of pharmacological effect have been observed after sublingual administration of captopril than oral route . Various pharmaceutical approaches have been made to design long acting devices to administer once a day formulation as controlled and sustained release systems to deliver the drug. The different methodologies applied and their limitations are described as follows.

Matrix tablets:

Various methods are available to formulate water soluble drugs into sustained release dosage forms by retarding the dissolution rate. One of the methods used to control the drug release and there by prolonging therapeutic activity is to use of hydrophilic or lipophilic polymers.

Coated tablets:

It is a classical technique to control the drug release. The drug has cross the barriers before it reaches the physiological fluids. The type and composition of the barriers is the release determining step. Barriers are mainly composed of hydrophilic or hydrophobic polymers and that is due to the compatibility of these

substances beside their in vivo safety even when used in large amounts.

Floating tablets:
These systems were used to prolong the gastric residence time of drug delivery systems. They remain buoyant in the stomach for prolonged period of time without affecting the gastric emptying rate of other contents. A floating dosage form is useful for those drugs that act locally in the proximal gastro intestinal tract (GIT), are unstable in lower parts of GIT, or are poorly absorbed in the intestine.

Slow release granules and Sustained release oily matrix:
Stulzer et al developed the captopril granules of controlled release with different polymers as ethyl cellulose, ethyl/methyl cellulose and immediate release with polyvinyl pyrrolidone by fluid bed drier technique. The dissolution profile of granules coated with ethyl cellulose showed a median time release of 4hrs whereas for granules coated with ethyl/methyl cellulose was 3.5hrs. The blockage of angiotensin I-induced hypertensive effect lasted 8 hr in granules coated with PVP and of more than 12 hr in the granules coated with ethyl cellulose and ethyl/methylcellulose.

Sustained release microparticles:
Microparticles are small solid particulate carriers containing dispersed drug particles either in solution or crystalline form. They are made from natural and synthetic polymers. Dandagi et al worked on microparticles of Captopril using bovine serum albumin as a drug carrier prepared by emulsification-heat stabilization technique. The in vitro study of captopril loaded microparticles showed release of drug up to 24hrs. The invivo result showed preferential drug targeting towards liver, lungs, spleen and kidneys.

Mucoadhesive microcapsules:
The adhesive properties of certain types of polymer could be used to increase the residence time of orally administered drugs. A fuller understanding of the molecular processes underpinning such Mucoadhesive phenomena will help in the optimal design of the delivery systems. [4]

Rational for developing of SRDDS:
I. Formulation of SRDDS minimizes dosing frequency and sustained release provides availability of a drug at action site throughout the treatment to improve clinical efficiency of a drug molecule.
II. To reduce cost of treatment by reducing number of dosage requirement.
III. To minimize toxicity due to overdose which is often in conventional dosage from.
IV. To enhance the activity duration of a drug possessing short half-life.

Principle of SRDDS:
The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme. The absorption pool represents a solution of the drug at the site of absorption, Kr, Ka and Ke - first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. For non-immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. The drug release from the dosage form should follows zero-order kinetics, as shown by the following equation:
Kr° = Rate In = Rate Out = Ke.Cd.Vd----------1
Where,
Kr°: Zero-order rate constant for drug release-Amount/time
Ke: First-order rate constant for overall drug elimination-time
Cd: Desired drug level in the body – Amount/volume
Vd: Volume space in which the drug is distributed in litter

Challenges for SRRDS:
Dose dumping:
This can greatly increase the concentration of a drug in the body and there by produce adverse effects or even druginduced toxicity. Dose dumping means the relatively large quantity of medication in a sustained release formulation is slowly released. If the dose dumping can leads to fatalities in case of potent drug, which have a narrow therapeutic, index e.g. Phenobarbital.

Limited choice of selecting desired dose in the unit:
In case of conventional dosage forms, the dose adjustments are much simple e.g. tablet can be divided into two portions. In case of sustained release dosage forms, this can appear to be much more complicated. Sustained release property may get lost, if dosage form is fractured.

Poor *in-vitro* – *in-vivo* correlation:
In sustained release dosage form, the rate of drug release is slowly reduced to achieve drug release possibly over a large region of gastrointestinal tract. Hence it is so called as 'Absorption window' becomes important and give rise to unsatisfactory drug

absorption in-vivo despite excellent in-vitro release characteristics.

Patient variation:
The time period required for absorption of drug released from the dosage form may vary among individuals. The coadministration of other drugs, presence or absence of food and residence time in gastrointestinal tract is different among patients. This also gives rise to variation in clinical response among the patient.

MATERIALS:

Aceclofenac-Provided by SURA LABS, Dilsukhnagar, Hyderabad, Sodium Alginate-Merck Specialities Pvt Ltd, Mumbai, India, Eudragit RLPO-Merck Specialities Pvt Ltd, Mumbai, India, Lactose-Merck Specialities Pvt Ltd, Mumbai, India,Magnesium stearate-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India.

METHODOLOGY:

Analytical method development:
Buffer Preparation:
Preparation of 0.2 M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.218 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000mL of distilled water and mixed.

Preparation of 0.2M sodium hydroxide solution: Accurately weighed 8 gm sodium hydroxide pellets were dissolved 1000ml of distilled water and mixed.

Preparation of pH 6.8 Phosphate buffer: Accurately measured 250ml of 0.2M potassium Dihydrogen ortho phosphate and 112.5 ml 0.2M NaOH was taken into the 1000ml volumetric flask. Volume was made up to 1000ml with distilled water.

Determination of Wavelength:
10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution again 1ml was taken it in to another volumetric flask and made it up to 10 ml with media (working solution - 10µg/ml). The working solution was taken for determining the wavelength.

Determination of Calibration Curve:
10mg of pure drug was dissolved in 10ml methanol (primary stock solution - 1000 µg/ml). From this primary stock solution 1 ml was pipette out into 10 ml volumetric flask and made it up to 10ml with the media (Secondary stock solution – 100µg/ml). From secondary stock solution required concentrations were prepared (shown in Table 8.1 and 8.2) and those concentrations absorbance were found out at required wavelength.

Preformulation parameters
The quality of tablet, once formulated by rule, is generally dictated by the quality of physicochemical properties of blends. There are many formulations and process variables involved in mixing and all these can affect the characteristics of blends produced. The various characteristics of blends tested as per Pharmacopoeia.

Angle of repose:
The frictional force in a loose powder can be measured by the angle of repose. It is defined as, the maximum angle possible between the surface of the pile of the powder and the horizontal plane. If more powder is added to the pile, it slides down the sides of the pile until the mutual friction of the particles producing a surface angle, is in equilibrium with the gravitational force. The fixed funnel method was employed to measure the angle of repose. A funnel was secured with its tip at a given height (h), above a graph paper that is placed on a flat horizontal surface. The blend was carefully pored through the funnel until the apex of the conical pile just touches the tip of the funnel. The radius (r) of the base of the conical pile was measured. The angle of repose was calculated using the following formula:

Formulation composition for tablets

INGREDIENTS (mg)	FORMULATION CODE							
	F1	F2	F3	F4	F5	F6	F7	F8
Aceclofenac	100	100	100	100	100	100	100	100
Sodium Alginate	20	40	60	80	-	-	-	-
Eudragit RLPO	-	-	-	-	20	40	60	80
Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Magnesium stearate	5	5	5	5	5	5	5	5
Talc	3	3	3	3	3	3	3	3
Total Weight	200	200	200	200	200	200	200	200

All the quantities were in mg

RESULTS AND DISCUSSION:

The present study was aimed to developing sustained release tablets of Aceclofenac using various polymers. All the formulations were evaluated for physicochemical properties and *in vitro* drug release studies.

Analytical Method:

Graphs of Aceclofenac were taken in 0.1N HCL and in pH 6.8 phosphate buffer at 274 nm and 276 nm respectively.

Table : Observations for graph of Aceclofenac in 0.1N HCL

Concentration (µg/ml)	Absorbance
0	0
2	0.127
4	0.243
6	0.341
8	0.467
10	0.568

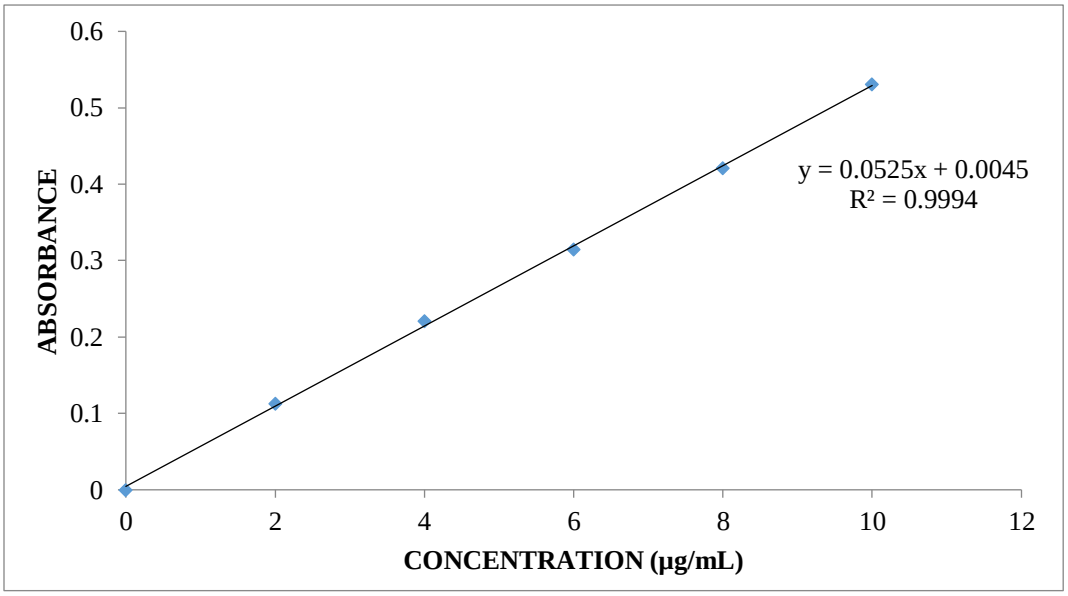

Fig: Standard curve of Aceclofenac

Table : Standard graph values of Aceclofenac at 276 nm in pH 6.8 phosphate buffer

Concentration (µg/ml)	Absorbance
0	0
2	0.113
4	0.221
6	0.315
8	0.421
10	0.531

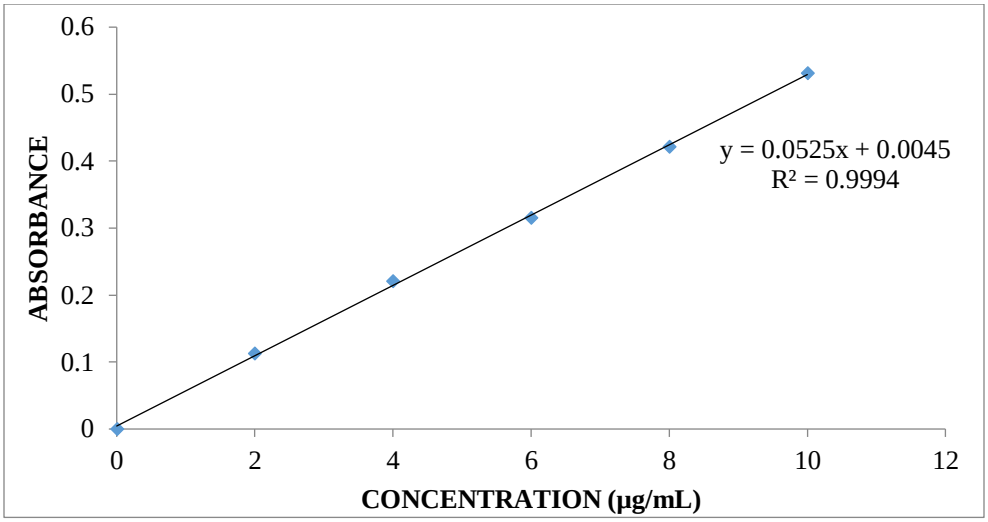

Fig : Standard curve of Aceclofenac

Preformulation parameters of powder blend:

Table : Pre-formulation parameters of Core blend

Formulation Code	Angle of Repose	Bulk density (gm/mL)	Tapped density (gm/mL)	Carr's index (%)	Hausner's Ratio
F1	33º01' ±1.18	0.22 ± 0.02	0.25 ± 0.25	13.10 ± 1.14	1.15± 0.15
F2	30º01'± 1.37	0.25 ± 0.02	0.29 ± 0.04	13.32 ± 5.22	1.15 ± 0.07
F3	31º09'±2.12	0.26 ± 0..03	0.29 ± 0.02	10.44 ± 3.94	1.11 ± 0.05
F4	34º06' ±0.53	0.27± 0.06	0.31 ± 0.07	11.83 ± 2.85	1.13 ± 0.03
F5	34 º17'±1.0	0.23 ± 0.01	0.28 ± 0.01	17.04 ± 2.82	1.20 ± 0.04
F6	32º29' ±0.91	0.29 ± 0.01	0.33 ± 0.01	7.09 ± 2.82	1.13 ± 0.03
F7	33º21' ±0.83	0.24 ± 0.03	0.27 ± 0.03	11.22 ± 4.21	1.12 ± 0.05
F8	33º28'±0.83	0.28 ± 0.01	0.31 ± 0.05	11.55 ± 3.52	1.13 ± 0.04

All the values represent n=3

Tablet powder blend was subjected to various pre-formulation parameters. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.22 ± 0.02 to 0.29 ± 0.01 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.25 ± 0.25 to 0.33 ± 0.01 showing the powder has good flow properties. The compressibility index of all the formulations was found to be below 17.04 which show that the powder has good flow properties. All the formulations has shown the hausners ratio ranging between 1.11 to 1.20 indicating the powder has good flow properties.

Quality control parameters for tablets:

Tablet quality control tests such as weight variation, hardness, friability, thickness, and drug release studies in different media were performed on the compressed tablet.

Table : *In vitro* quality control parameters for tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	199.52	4.9	0.36	3.12	97.15
F2	200.12	4.6	0.52	3.26	99.34
F3	198.91	5.0	0.41	3.43	98.72
F4	200.01	4.8	0.64	3.51	98.31
F5	200.09	5.1	0.38	3.64	96.80
F6	199.87	4.3	0.60	3.49	97.60
F7	198.35	4.8	0.48	3.57	98.25
F8	199.29	4.5	0.53	3.29	99.62
F9	200.21	4.7	0.49	3.42	97.42

Weight variation test:

Tablets of each batch were subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet. The average weight of the tablet is approximately in range of 198.35 to 200.21 mg, so the permissible limit is ±7.5% (>200 mg). The results of the test showed that, the tablet weights were within the pharmacopoeia limit.

Hardness test:

Hardness of the three tablets of each batch was checked by using Pfizer hardness tester and the data's were shown in Table 8.4. The results showed that the hardness of the tablets is in range of 4.3 to 5.1 kg/cm^2, which was within IP limits.

Thickness:

Thickness of three tablets of each batch was checked by using Micrometer and data shown in Table-8.4. The result showed that thickness of the tablet is raging from 3.12 to 3.64 mm.

Friability:

Tablets of each batch were evaluated for percentage friability and the data were shown in the Table 8.4. The average friability of all the formulations was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

Drug content:

Drug content studies were performed for the prepared formulations. From the drug content studies it was concluded that all the formulations were showing the % drug content values within 96.80 -99.62 %.

All the parameters such as weight variation, friability, hardness, thickness and drug content were found to be within limits.

***In Vitro* Drug Release Studies**

Table: Dissolution data of Aceclofenac tablets

TIME (H)	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
1	17.36	14.53	10.90	9.48	14.99	13.81	10.93	08.38
2	23.02	18.90	16.32	11.15	20.53	18.96	16.15	11.69
3	30.68	24.06	21.41	17.86	27.60	26.71	20.68	18.19
4	36.82	28.20	25.06	22.32	33.12	35.56	27.14	24.43
5	41.69	36.89	32.26	31.91	36.24	40.12	34.39	29.37
6	47.25	41.32	37.11	35.15	40.71	43.90	38.71	35.65
7	52.03	48.86	45.51	41.63	47.68	51.18	42.52	40.97
8	66.19	57.17	54.64	48.27	55.92	57.21	48.10	48.21
9	72.01	61.95	58.38	52.14	69.15	62.19	54.98	52.10
10	83.92	75.61	66.92	62.70	72.76	68.11	57.71	57.78
11	90.86	83.46	71.46	69.31	88.40	86.07	67.50	65.86
12	96.42	89.82	78.19	73.13	99.62	92.46	77.86	70.15

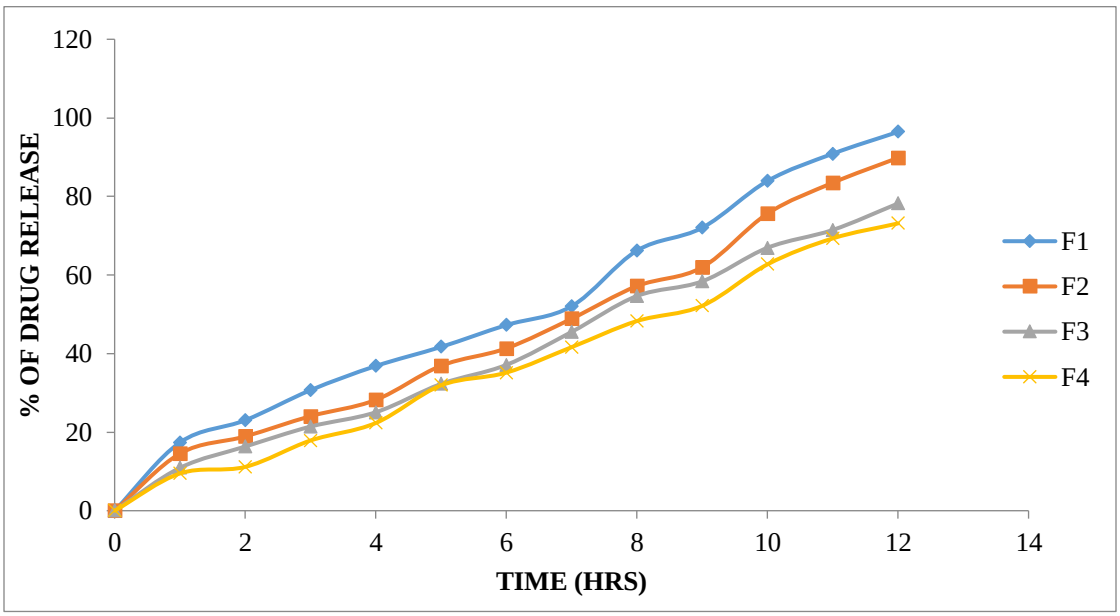

Fig : Dissolution profile of Aceclofenac (F1, F2, F3 and F4 formulations)

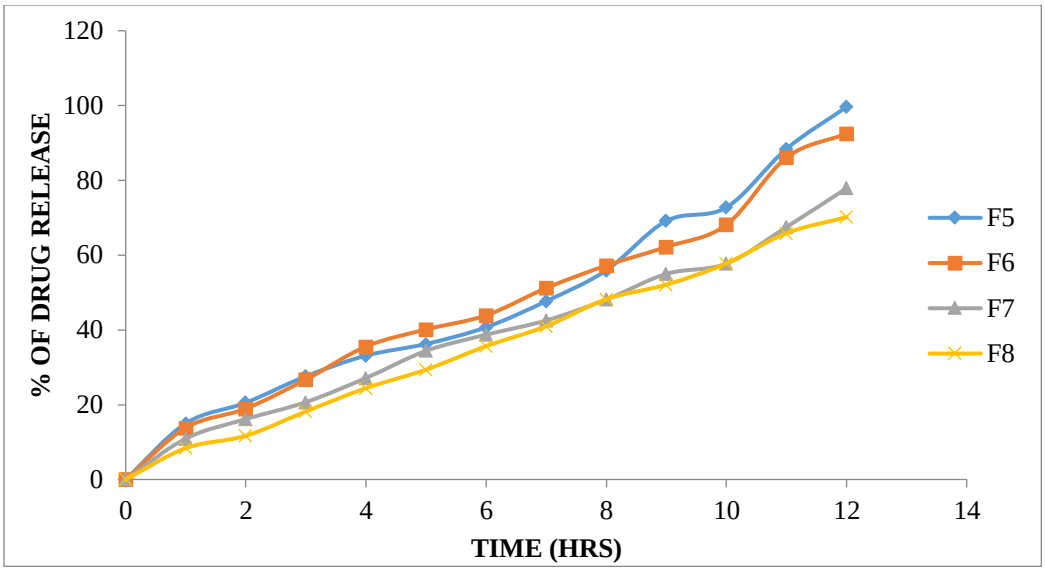

Fig: Dissolution profile of Aceclofenac (F5, F6, F7 and F8 formulations)

From the dissolution data it was evident that the formulations prepared with Sodium Alginate as polymer were retarded the drug release more than 12 hours.

Whereas the formulations prepared with Eudragit RLPO retarded the drug release up to 12 hours in the concentration 20 mg. In higher concentrations the polymer was unable to retarded the drug release.

Hence from the above dissolution data it was concluded that F5 formulation was considered as optimised formulation because good drug release (99.62%) in 12 hours.

Application of release rate kinetics to dissolution data:

Data of *in vitro* release studies of formulations which were showing better drug release were fit into different equations to explain the release kinetics of Aceclofenac release from Sustained tablets. The data was fitted into various kinetic models such as zero, first order kinetics; higuchi and korsmeyer peppas mechanisms and the results were shown in below table.

Table: Release kinetics data for optimized formulation (F5)

CUMULATIVE (%) RELEASE Q	TIME (T)	ROOT (T)	LOG(%) RELEASE	LOG (T)	LOG (%) REMAIN	RELEASE RATE (CUMULATIVE % RELEASE / t)	1/CUM% RELEASE	PEPPAS log Q/100	% Drug Remaining	Q01/3	Qt1/3	Q01/3-Qt1/3
0	0	0			2.000				100	4.642	4.642	0.000
14.99	1	1.000	1.176	0.000	1.929	14.990	0.0667	-0.824	85.01	4.642	4.397	0.245
20.53	2	1.414	1.312	0.301	1.900	10.265	0.0487	-0.688	79.47	4.642	4.299	0.342
27.6	3	1.732	1.441	0.477	1.860	9.200	0.0362	-0.559	72.4	4.642	4.168	0.474
33.12	4	2.000	1.520	0.602	1.825	8.280	0.0302	-0.480	66.88	4.642	4.059	0.582
36.24	5	2.236	1.559	0.699	1.805	7.248	0.0276	-0.441	63.76	4.642	3.995	0.647
40.71	6	2.449	1.610	0.778	1.773	6.785	0.0246	-0.390	59.29	4.642	3.899	0.742
47.68	7	2.646	1.678	0.845	1.719	6.811	0.0210	-0.322	52.32	4.642	3.740	0.901
55.92	8	2.828	1.748	0.903	1.644	6.990	0.0179	-0.252	44.08	4.642	3.532	1.109
69.15	9	3.000	1.840	0.954	1.489	7.683	0.0145	-0.160	30.85	4.642	3.136	1.505
72.76	10	3.162	1.862	1.000	1.435	7.276	0.0137	-0.138	27.24	4.642	3.009	1.633
88.4	11	3.317	1.946	1.041	1.064	8.036	0.0113	-0.054	11.6	4.642	2.264	2.378
99.62	12	3.464	1.998	1.079	-0.420	8.302	0.0100	-0.002	0.38	4.642	0.724	3.917

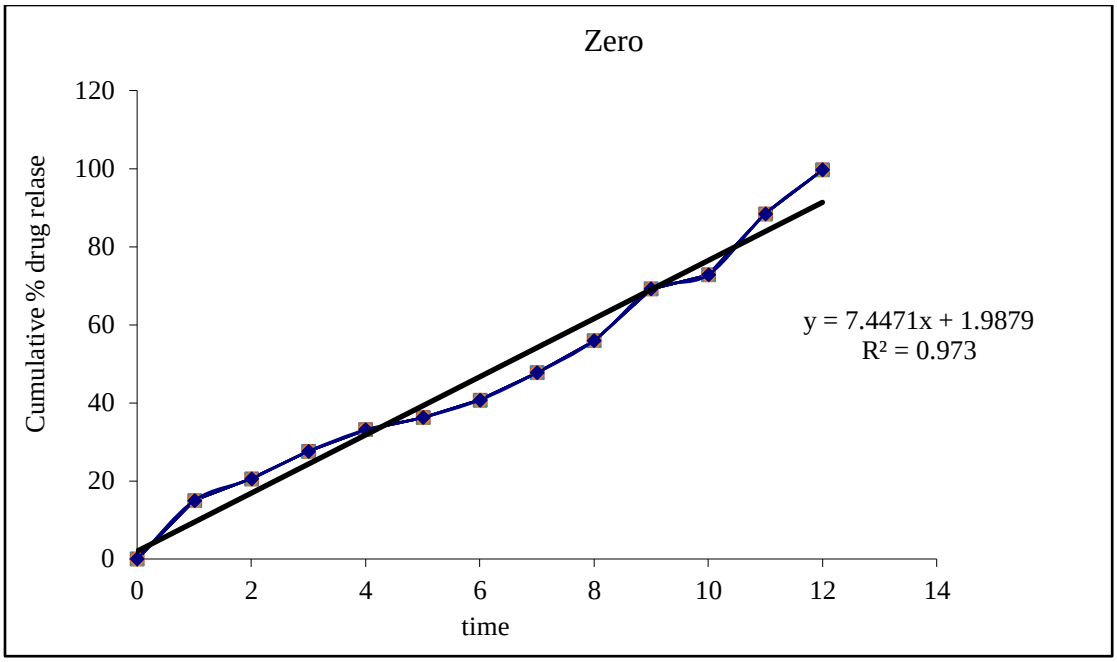

Figure: Graph of zero order kinetics

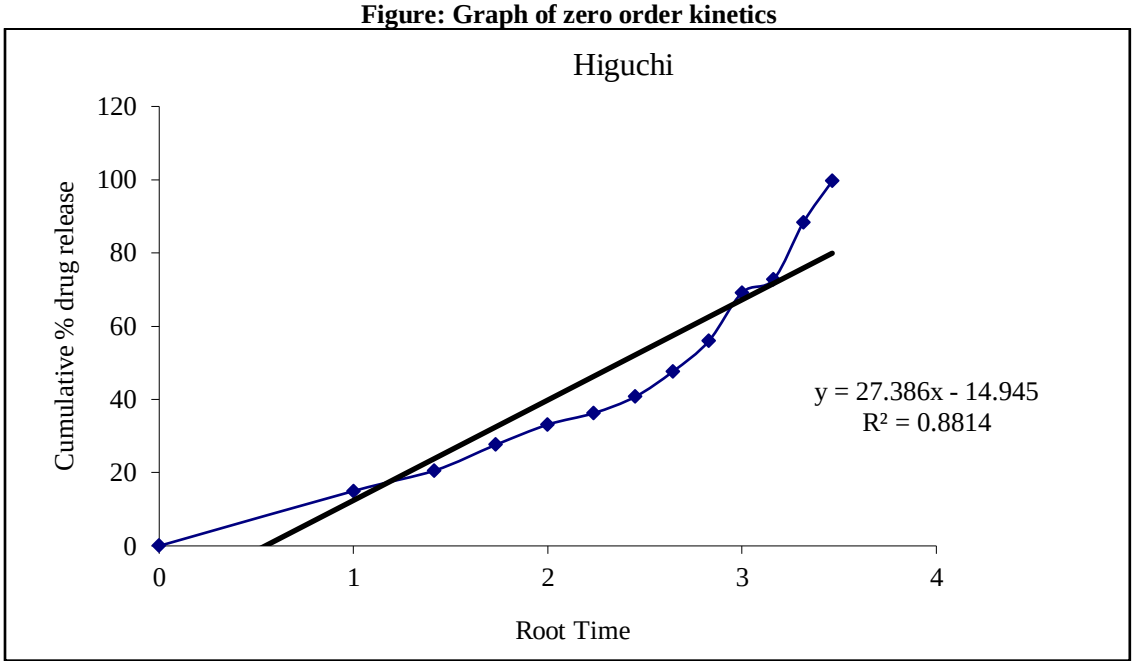

Figure: Graph of higuchi release kinetics

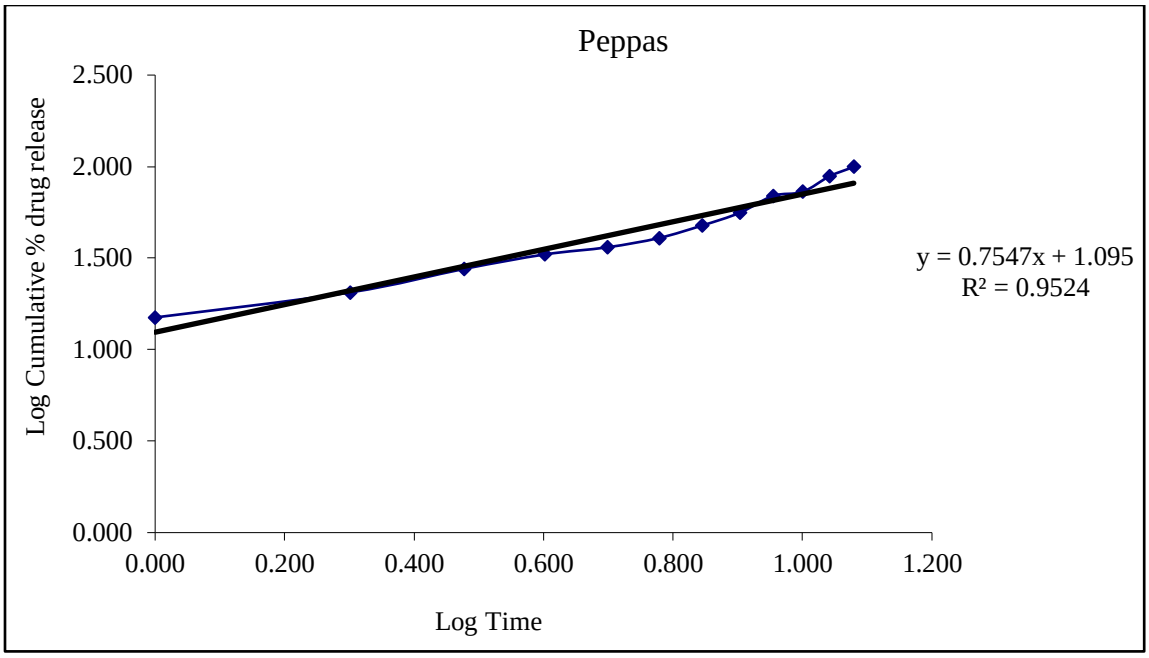

Figure : Graph of Peppas release kinetics

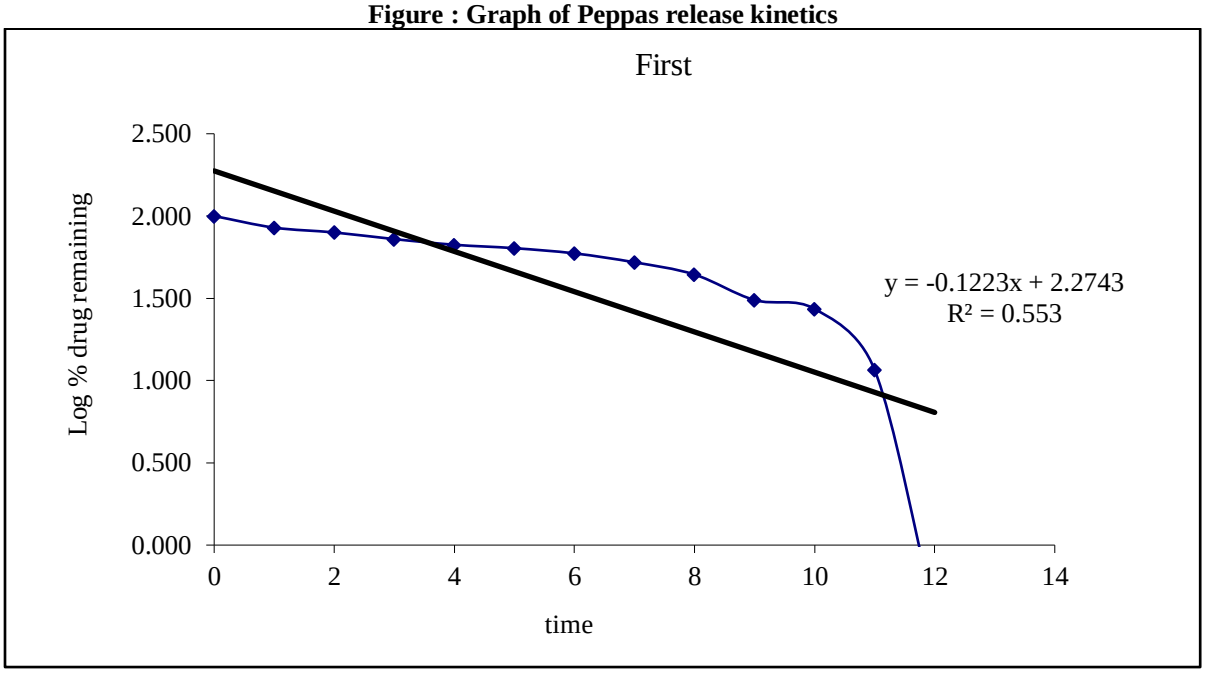

Figure : Graph of First Order Release Kinetics

Based on the data above results the optimized formulation followed Zero order kinetics.

Drug and excipient compatibility studies
FTIR STUDY

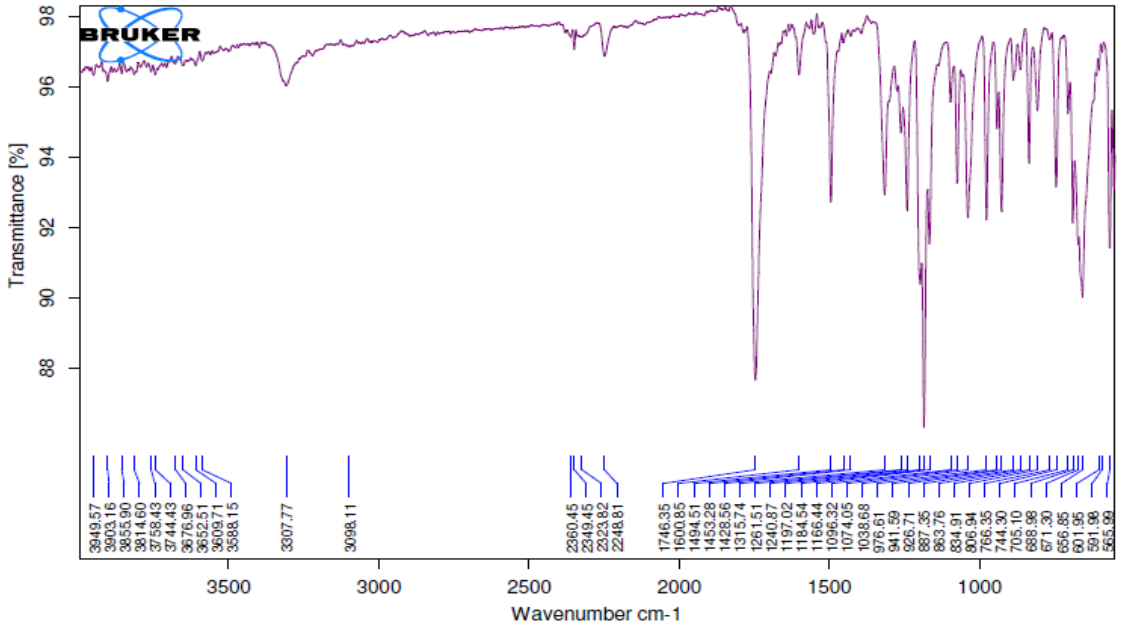

Fig: FTIR Graph of pure drug

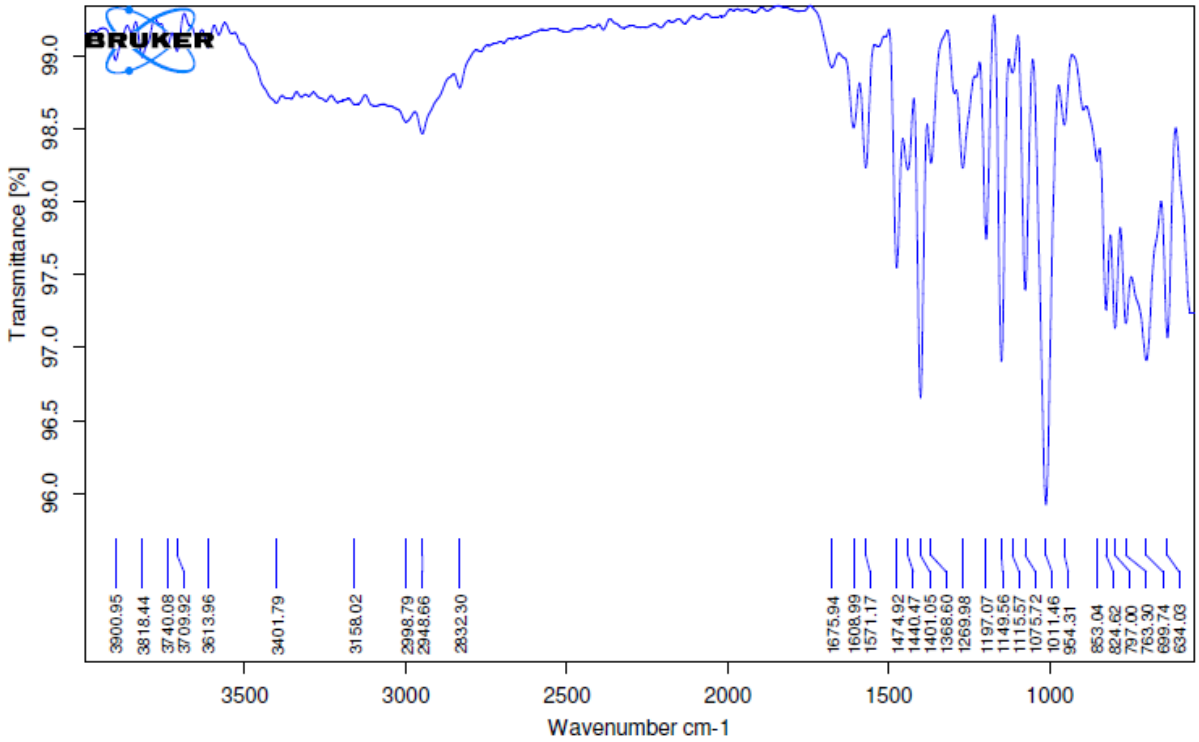

Fig: FTIR Graph of Optimised Formulation

From the FTIR data it was evident that the drug and excipients does not have any interactions. Hence they were compatible.

CONCLUSION:

The oral route of drug delivery is the most preferred route for administration of drugs. The rationale for the development of a sustained release formulation of a

drug is to enhance its therapeutic benefits, minimizing its side effect while improving the management of the diseased condition. Sustained drug delivery systems significantly improve the therapeutic efficacy of drugs. Drug-release-retarding polymers are the key performers in such systems.
Aceclofenac is a nonsteroidal anti-inflammatory drug (NSAID) analog of diclofenac. It is used for the relief of pain and inflammation in rheumatoid arthritis, osteoarthritis and ankylosing spondylitis.

FT-IR frequencies showed that the Aceclofenac used was similar to the reported values. After the comparison of FTIR results, it was concluded that there was no incompatibility between drug and polymers.

Polymers like Sodium Alginate and Eudragit RLPO were chosen as polymers for the formation of sustained release matrix tablets.

In this study, nine formulations were prepared by direct compression method using different polymers at varying ratios.

Each batch of the formulations was evaluated for pre-compression parameters such as bulk density, tapped density, the angle of repose, compressibility index and Hausner's ratio and the results were within the limit. The prepared formulations were also evaluated for hardness, friability, weight variation, content uniformity and in-vitro drug release studies.

Formulation F5 showed sustained drug release for 12 hours so it was selected as the best formulation among all the nine formulations. The kinetics of drug release was best explained by Zero order kinetics.

Based on the above evaluation studies, it could be concluded that taken polymers can be used as a suitable matrix forming agent by direct compression method for sustained release of Aceclofenac over 12 hr by providing reduced dosing frequency and side effects.

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