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FORMULATION AND EVALUATION OF BILAYER TABLETS OF ACECLOFENAC AND ALLOPURINOL

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INTRODUCTION

Oral Drug Delivery

Despite phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration, the unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. There are of course many applications and large markets for non-oral products and the technologies that deliver them. However, if it is a viable option, oral drug delivery will be chosen in all but the most exceptional circumstances. Moreover, if the oral route is not immediately viable, pharmaceutical companies will often invest resources in making it viable, rather than plumping for an alternative delivery method.[1,2,3,4] drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from a polymer chain.

Immediate Release Drug Delivery System

Introduction: Immediate release drug delivery system is a conventional type of drug delivery. It is designed to disintegrate and release their medicaments with no special rate controlling features.

These are the dosage forms in which ≥85% of labeled amount dissolves with in 30min.

However for immediate release tablets, tablet disintegrants play an important role in ensuring that the tablet matrix break up on contact with fluid in the stomach to allow the release the active drug which then become available in whole or in part, for absorption from GIT.

Mechanism of Drug Release: On exposure to aqueous fluids, hydrophilic matrices take up water and the polymer starts hydrating to from a gel layer. Drug release is controlled by

diffusion barriers/by erosions. An intial burst of soluble drug may occur due to surface leaching when a matrix containing a swellable glassy polymer comes in to contact with an aqueous medium, there is an abrupt change from a glassy to rubbery state associate with swelling process with time, water infiltration deep in to a case increasing the thickness by the gel layer. The outer layer become fully hydrated and starts dissolving or eroding. When water reaches the centre of the system and the concentration of drug falls below the solubility value, the release rate of the drug begins toreduce. At the same time an increase in thickness of the barrier layer with time increases the diffusion path length, reducing the rate of drug release.

Advantages Immediate Release Drug Delivery Systems

1. Improved compliance/added convenience.
2. Improved stability.
3. Suitable for controlled/sustained release actives.
4. Allows high drug loading.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging machinery.
7. Cost- effective.

Super Disintegrants in Immediate Release

These are especially important for an immediate release product where rapid release of drug substance is required. A disintegrant can be added to powder blend for direct compression.

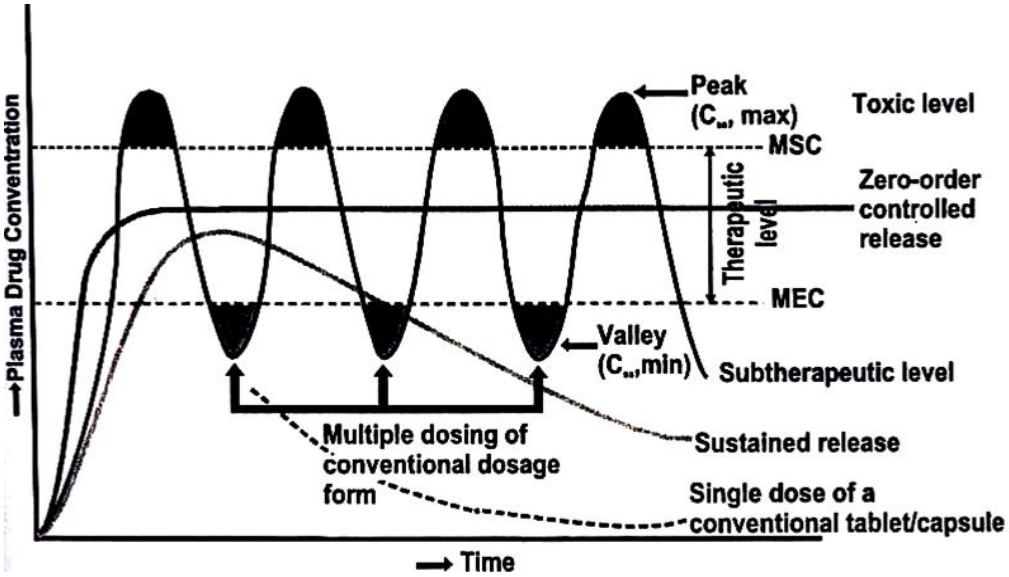


Figure 1.1: A hypothetical plasma concentration–time profile from conventional multiple and single doses of sustained and controlled delivery formulations.

Potential advantages of sustained release systems

Avoid patient's compliance problems

1. Employ less total drug

a) Minimize or eliminate local side effects.

b) Minimize or eliminate systemic side effects.

c) Obtain less potentiation or reduction in drug activity with chronic use.

d) Minimize drug accumulation with chronic dosing.

3. Improve efficiency in treatment

a) Cures or controls condition more promptly.

b) Improves control of condition i.e., reduced fluctuation in drug level.

c) Improves bioavailability of some drugs.

d) Make use of special effects, e.g. sustained-release aspirin for morning relief of arthritis by dosing before bed time.

4. Economy i.e. reduction in health care costs. The average cost of treatment over an extended time period may be less, with less frequency of dosing, enhanced therapeutic benefits and reduced side effects. The time required for health care personnel to dispense and administer the drug and monitor patient is also reduced.[7,8,9,10]

Disadvantages

1) Decreased systemic availability in comparison to immediate release conventional dosage forms, which may be due to incomplete release, increased first-pass metabolism, increased instability, insufficient residence time for complete release, site specific absorption, pH dependent stability etc.
2) Poor in vitro-in vivo correlation.
3) Possibility of dose dumping due to food, physiologic or formulation variables or chewing or grinding of oral formulations by the patient and thus, increased risk of toxicity.

Manufacturing Methods of Tablets

- Direct compression.
- Wet granulation method.
- Dry granulation method.
- Fluidized bed granulation.

Synonyms: Bilayer tablets, multi-layer matrix tablets, bilayer caplets.

Definition

Dual release tablet is a unit compressed tablet dosage form intended for oral administration. It contains two parts in which one part having conventional or immediate release part another one is sustained or controlled release part.

Bi layer tablets

Several pharmaceutical companies are currently developing bilayer tablets, for a variety of reasons like patent extension, therapeutic marketing to name a few.

Applications

Used in the combination therapy.

- Used to deliver the loading dose and sustained dose of the same or different drugs.
- Used for bilayer floating tablet in which one layer is floating layer another one is release layer of the drug.
- Used to deliver the two different drugs having different release profiles.

Advantages

- Extension of a conventional technology.
- Potential use of single entity feed granules.

Separation of incompatible components

- Patient compliance is enhanced leading to improve drug regimen efficacy.
- Patient convenience is improved because fewer daily doses are required.compared to traditional delivery system.
- Maintain physical and chemical stability.
- Retain potency and ensure dose accuracy.

Disadvantages

- Adds complexity and bilayer rotatory presses are expensive.
- Insufficient hardness, Layer separation, reduced yield.
- Inaccurate individual layer weight control.
- Cross contamination between the layers.

Ideal properties for bilayer tablets press

- Preventing capping and separation of the two individual layers that constitute the bilayer tablet.
- Preventing cross-contamination between the two layers.
- Producing a clear visual separation between the two layers.
- High yield and accurate and individual weight control of the two layers.

Types of bilayer tablet press

1. Single sided tablet press.
2. Double sided tablet press.
3. Bilayer tablet press with displacement monitor

METHODOLOGY

Direct Compression Method

All the ingredients were passed through the sieve#40 followed by the other ingredients were passed the same sieve. CCS, SSG, Cp, MCC, talc, were taken in a poly bag and mixed for 5minutes to ensure uniform mixing of the ingredients. Then the granules were dried in Hot air oven samples were removed randomly at different time intervals from the total bulk of the granules and then checked out for moisture content. The materials were passed through the sieve#22. Then magnesium stearate, talc, Colouring agents were added and compressed as Immediate release tablet.

Method of preparation and characterization of powder blend

Table 7: Composition of Sustained release tablet formulation.

Ingradients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Aceclofenac	100	100	100	100	100	100	100	100	100
HPMCK4m	25	50	75						
HPMCK15m				25	50	75			
HPMCK100m							25	50	75
MCC	117	92	67	117	92	67	117	92	67
Magnasium Stearate	4	4	4	4	4	4	4	4	4
Talc	4	4	4	4	4	4	4	4	4
Total wt	250	250	250	250	250	250	250	250	250

*All the quantities are expressed as mg per tablet.

Table 8: Composition of Immediate release tablet formulation.

Ingradients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Allopurinol Hydrochloride	50	50	50	50	50	50	50	50	50
CCS	6.25	12.5	25						
SSG				6.25	12.5	25			
Cross Povidone							6.25	12.5	25
MCC	39.75	33.5	21	39.75	33.5	21	39.75	33.5	21
Magnasium Stearate	2	2	2	2	2	2	2	2	2
Talc	2	2	2	2	2	2	2	2	2
Total wt	100	100	100	100	100	100	100	100	100

*All the quantities are expressed as mg per tablet.

Compression of Powder Blends Into Tablets

After evaluation of powder blend Immediate release tablets and sustained release tablets were prepared by Direct Compression granulation method using (4mm diameter, round flat faced punches) multiple punch tablet compression machine. Each tablet contained 250mg of Aceclofenac and 100mg of Allopurinol, the batch size for each formulation was 10 tablets.

RESULT AND DISCUSSION

PREFORMULATION PARAMETERS

Physicochemical parameters of drug

Organoleptic properties

Odourless, white or almost white crystalline powder

Melting point

Melting point values of Aceclofenac sample was found to be in range of 185^0C to 189^0C. The reported melting point range for Aceclofenac is 183.5^0C to 184^0C. Hence, experimental values are in good agreement with official values.

Solubility study

Table 12: The solubility of Aceclofenac in various solvents.

Name of solvent	Inference
Distilled water	Freely soluble
Methanol	Very soluble
Iso propyl alcohol	Soluble
Acetonitrile	Sparingly soluble
Acetone	Slightly soluble
Chloroform	Slightly soluble
0.1N HCl	Soluble
0.01N HCl	Soluble
Phosphate buffer(pH6.8)	Soluble

Analytical methods

λ max Determination

The absorption maximum for Aceclofenac was found to be 237nm.

Preparation of standard graph of Aceclofenac

Preparation of standard graph of Aceclofenac in 0.1N HCl

UV absorption spectrum of Aceclofenac in 0.1N HCl shows λ max at 237nm. Absorbances obtained for various concentrations of Aceclofenac in 0.1N HCl are given in table no 6.2. The graph of absorbance vs concentration for Aceclofenac was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml.

Preparation of standard graph of Aceclofenac in p^H 6.8 Phosphate buffer

UV absorption spectrum of Aceclofenac in p^H 6.8 Phosphate buffer shows λ max at 238nm. Absorbances obtained for various concentrations of Aceclofenac in p^H 6.8 phosphate buffer are given in table no.6.3. The graph of absorbance vs concentration for Aceclofenac was found to be linear in the concentration range of 2-16 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-16 µg /ml.

Table 13: Data of Concentration and Absorbance for in Aceclofenac 0.1N HCl.

S.No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.118
3	4	0.276
4	6	0.452
5	8	0.796
6	10	0.982
7	12	1.089
8	14	1.181

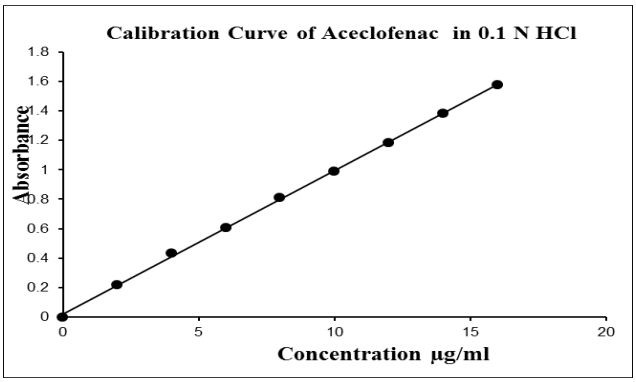


Figure 7: Standard graph of Aceclofenac 0.1N HCl.

Table 14: Data of concentration and absorbance for Aceclofenac pH 6.8 phosphate buffer.

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.121
3	4	0.267
4	6	0.471
5	8	0.692
6	10	0.875
7	12	1.097
8	14	1.175

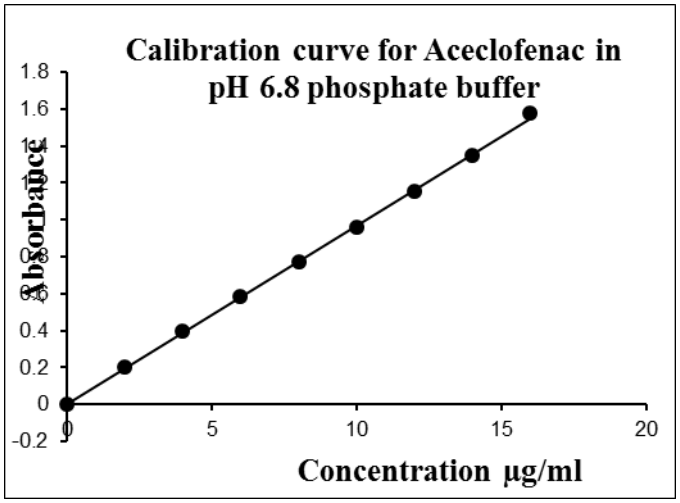
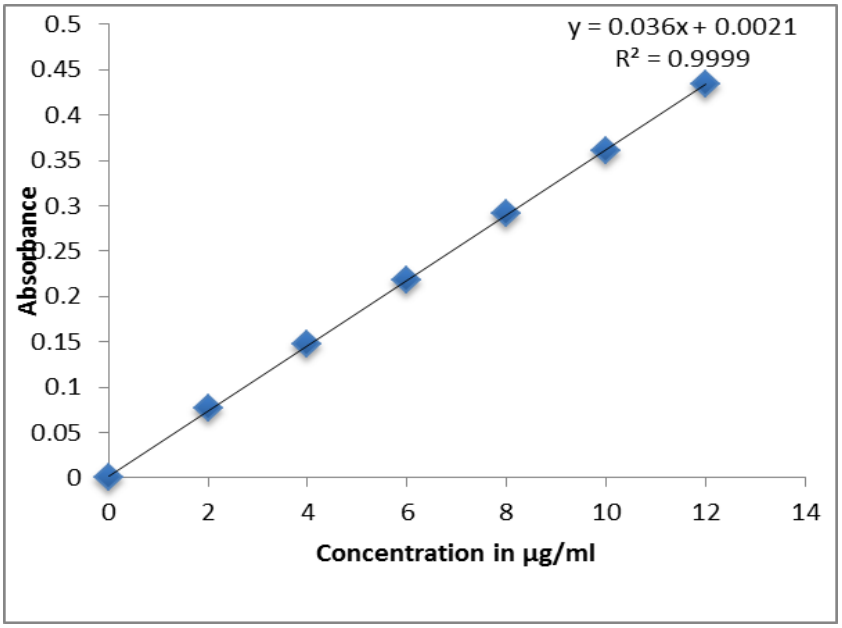


Figure 8: Standard graph of Methocabamol in 6.8 buffer.

Preparation of standard graph of Allopurinol in p^H 6.8 Phosphate buffer

UV absorption spectrum of Allopurinol in p^H 6.8 Phosphate buffer shows λ max at 286nm. Absorbances obtained for various concentrations of Allopurinol in p^H 6.8 phosphate bu in p^H 6.8 phosphate buffer are given in table no.6.3. The graph of absorbance vs concentration for Allopurinol was found to be linear in the concentration range of 2-8 µg /ml. The drug obeys Beer- Lambert's law in the range of 2-8µg /ml.

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	2	0.065
3	4	0.134
4	6	0.265
5	8	0.318
6	10	0.375
7	12	0.442



Evaluation of Sustained Release Tablet

Table 17: Physico-chemical characterization of Aceclofenac tablets.

S.no	Formulation	Weight variation	Thickness	Hardness	Friability	Disintegration Time
1	F1	0.398	1.5	4	0.26	0.26
2	F2	0.415	1.6	4	0.62	0.62
3	F3	0.395	1.7	4.5	0.78	0.78
4	F4	0.413	1.6	4	0.79	0.79
5	F5	0.407	1.5	4.5	0.41	0.41
6	F6	0.386	1.6	4	0.38	0.38
7	F7	0.394	1.5	4	0.35	0.35
8	F8	0.405	1.6	4.5	0.36	0.36
9	F9	0.412	1.5	4.5	0.29	0.29

Table 18: Physico-chemical characterization of Allopurinol tablets.

Sno	Formulation	Weight variation	Thickness (mm)	Hardness (Kg/Cm^2)	Friability %	Disintegrating Time (sec)
1	F1	0.472	2.1	2.8	0.34	43
2	F2	0.765	2.1	2.6	0.37	47
3	F3	0.646	2.3	2.9	0.27	53
4	F4	0.629	2.3	2.6	0.32	40
5	F5	0.685	2.3	2.5	0.43	34
6	F6	0.704	2.2	2.8	0.34	43
7	F7	0.698	2.2	2.6	0.37	45
8	F8	0.712	2.1	2.5	0.34	47
9	F9	0.694	2.2	2.6	0.37	49

6.2.5. *In-vitro* dissolution studies

Table 6.6: Dissolution data of formulations.

Time (hours)	Dissolution medium	% Drug release of F1	% Drug release of F2	% Drug release of F3	% Drug release of F4	% Drug release of F5	% Drug release of F6	% Drug release of F7	% Drug release of F8	% Drug release of F9
0	0.1 N HCl	0	0	0	0	0	0	0	0	0
0.5		12.43	5.16	3.16	5.89	13.46	5.12	3.79	8.56	13.49
1		21.65	13.46	9.19	11.29	25.54	11.25	9.46	18.64	23.76
1.5		30.21	2079	15.46	24.57	31.48	19.21	16.48	26.79	31.49
2		40.77	31.48	22.78	31.87	38.49	25.89	27.64	34.67	44.19
3	pH 6.8 phosphate bufffer	46.10	46.19	29.16	39.46	45.76	36.19	35.57	44.59	50.73
4		54.69	59.87	38.46	45.21	57.49	45.73	43.58	57.19	64.18
5		65.87	67.46	44.59	52.34	66.87	56.79	56.78	64.28	74.46
6		75.63	78.46	50.76	60.79	79.47	62.49	69.47	79.49	88.46
7		83.61	88.76	60.46	65.16	88.87	70.23	75.89	88.46	99.91
8		95.89		65.16	72.46	100.78	79.45	85.46	99.76	
9		100.69		69.46	80.77		87.74	99.46		
10				72.46	98.47		98.16			

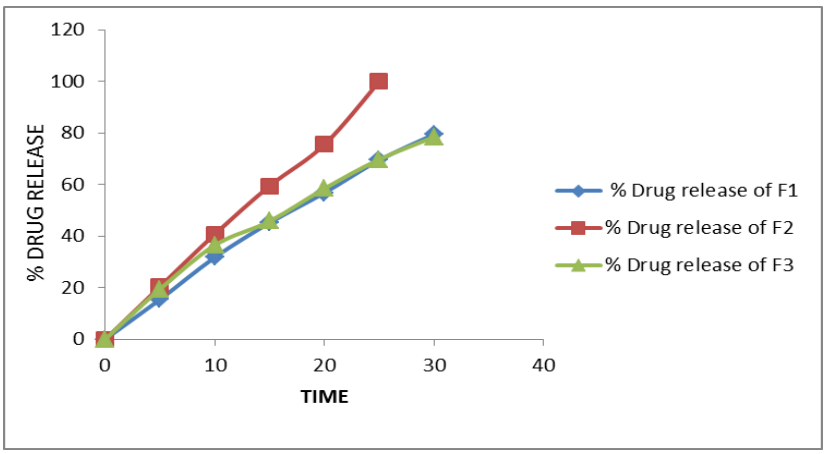


Fig: % drug release of formulation F1,F2,F3.

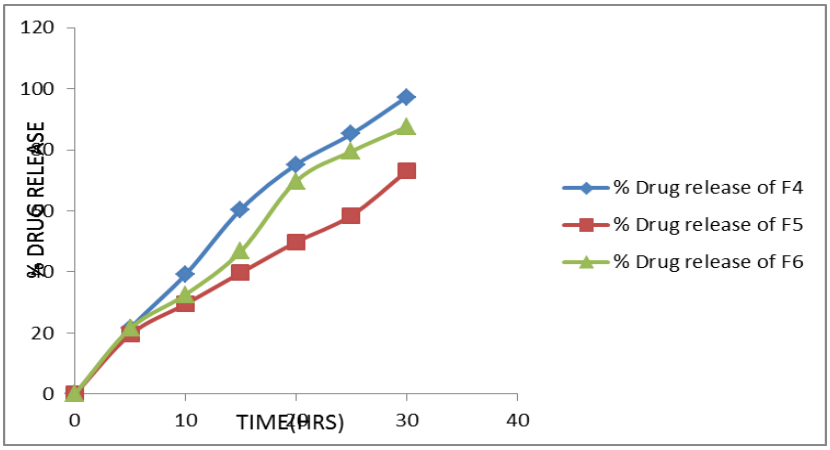


Fig: % drug release of formulation F4,F5,F6.

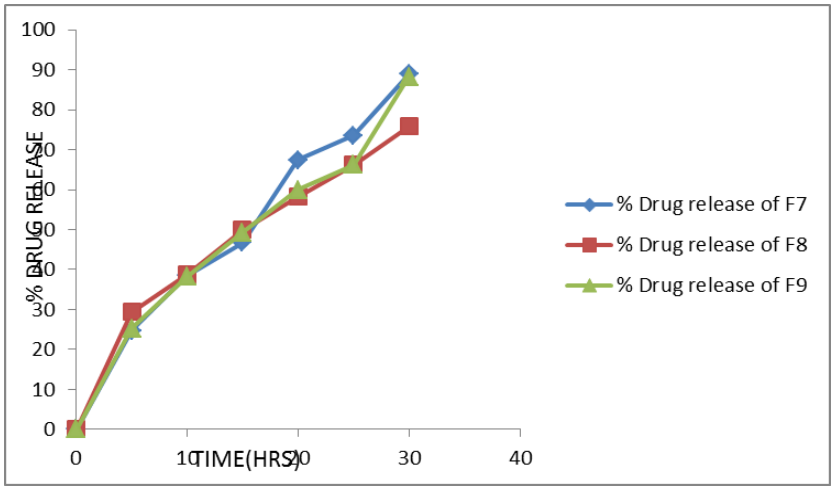
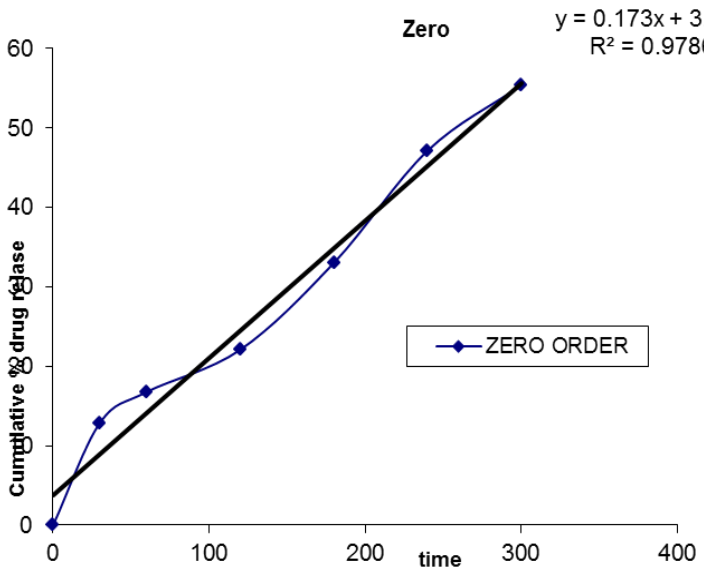


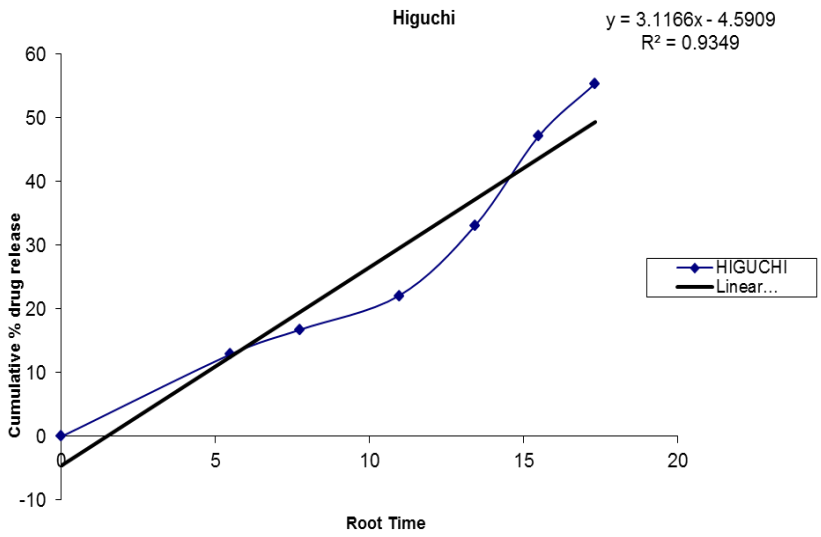
Fig: % drug release of formulation F7,F8,F9.

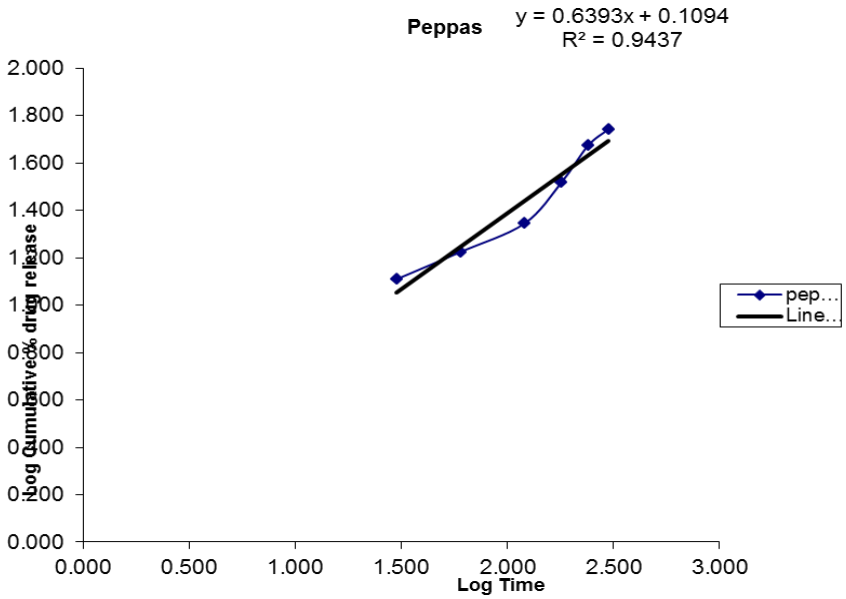
Various sustained release formulations were formulated with HPMC K4M, K15M, K100M, polymer alone; and microcrystalline cellulose was used as diluents. The drug release data of dissolution studies of formulation f4 containing HPMC K100M is shown concentration levels were found to be 98.47% respectively.

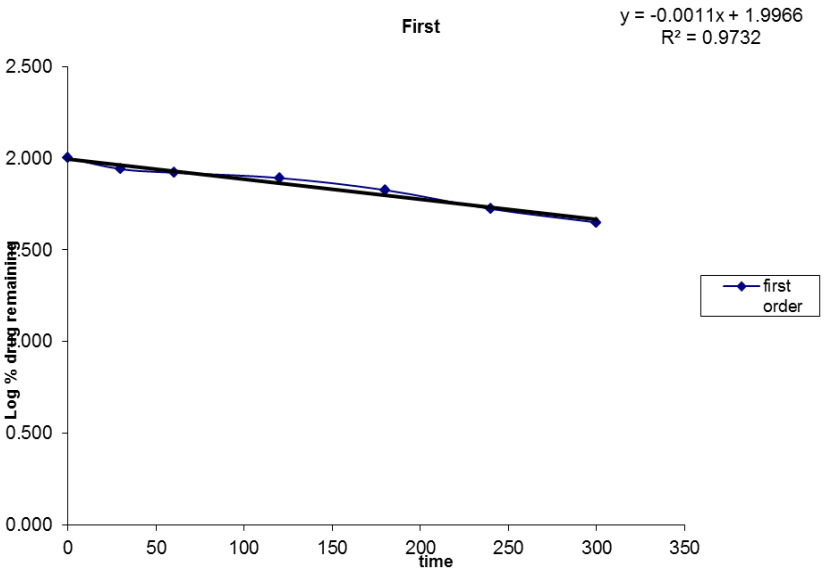
Different kinetic models for Aceclofenac Multi-Particulate Mini tablets

Code	Zero order		First order		Higuchi		Peppas		Best fit model
	R^2	K_0 mg/h^{-1}	R^2	K_1 (h^{-1})	R^2	K (mg $h^{-1/2}$)	R^2	n	
F8	0.9786	3.769	0.9349	0.1938	0.9732	23.8548	0.9437	1.9166	Peppas




Higuchi
y = 3.1166x - 4.5909
R² = 0.9349
Cumulative % drug release
Root Time
HIGUCHI
Linear...


Peppas
y = 0.6393x + 0.1094
R² = 0.9437
Log Cumulative % drug release
Log Time
pep...
Line...


First
y = -0.0011x + 1.9966
R² = 0.9732
Log % drug remaining
time
first order

CONCLUSION

The conclusions drawn from the present investigation were given below:

Suitable analytical method based on UV-Visible spectrophotometer was developed for Aceclofenac λ_{max} of 228 nm, 206nm were identified in 0.1N HCl and pH 6.8 Phosphate buffer.

The tablets were evaluated for pharmacopoeial and non-pharmacopoeial (industry specified) tests. Based on the results, F-8, F-3 were identified as better formulation amongst all formulations.

In vitro release profiles of optimized formulations of Aceclofenac F8 Formulation.

The conclusions arrived in this thesis indicated that the formulations of Aceclofenac sustained tablets in this investigation was found to be satisfactory based on *in vitro* release studies. Thus the objectives envisaged in this thesis were arrived.

The bioavailability of the drug can also be improved with this sustained drug delivery system which increase efficacy, compliance and better clinical usefulness of patients.

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