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FORMULATION AND EVALUATION OFANTIPLATELET AND ANTI THROMBOTIC IMMEDIATE RELEASE TABLETS

Mahendar Rupavath[1]* and Prof. K. S. K. Rao Patnaik[2]

[1]Research Scholar, College of Technology, Pharmaceutics Department, Osmania University, Hyderabad.

[2]College of Technology, Osmania University

Abstract:

Clopidogrel is a thienopyridine class inhibitor of P2Y12 adenosine 5'-diphosphate (ADP) platelet receptors and used to inhibit blood clots in coronary artery disease, peripheral vascular disease and cerebrovascular disease. Clopidogrel is a pro-drug of carboxyl clopidogrel activated in the liver by cytochrome P450 and CYP2C19 enzyme. The active metabolite has an elimination half-life of about 7-8 h and acts by forming a disulfide bridge with the platelet ADP receptor. All raw materials are weighed according to formula and sifted through the sieve #30. All sifted materials except Cutina HRPH are placed in octagonal blender and blended for 15min. All sifted materials, Cutina HRPH loaded into the octagonal blender and blended for 5min. Samples were taken from at least three places from the blender and the samples were sent to QC for in process analysis. After the QC approval the samples were subjected to tablet making. The blended material was compressed into tablets using rotary die apparatus as per SOP. Tablets were coated with the coating solution of Opadry II pink. 6 tablets were placed in each of 6 dissolution flasks containing 900 ml of pH 2.0 HCl maintained at 37±0.5°C. The apparatus was run for 30 minutes. A suitable volume of sample was withdrawn at regular intervals of time and filtered through 0.45 µm membrane filter. The absorbance of the sample preparations were measured at 249 nm, using pH 2.0 HCl as blank

***Corresponding Author:**

Mahendar Rupavath,

Research Scholar, College of Technology,
Pharmaceutics Department, Osmania University,
Hyderabad.

EMAiL: ***mahi1.rupavath@gmail.com***

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INTRODUCTION:

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for systemic effects. In addition oral medication is the first avenue investigated in the discovery and development of new drug entities and pharmaceutical formulations mainly because of patient acceptance, convenience in administration and cost effective manufacturing process. For many drug substances, conventional immediate release formulations provide clinically effective therapy while maintaining the required balance of pharmacokinetic and pharmacodynamic profiles with an acceptable level of safety to the patient [1-3].

Conventional IR formulations include fast disintegrating tablets and granules that use effervescent mixtures, sodium carbonate (sodium bicarbonate) and citric acid [4-6].

Many dosage forms are designed to release the drug immediately or at least as quickly as possible after administration. This is useful if a fast onset of action is required for therapeutic reasons. For example, a tablet containing a painkiller should disintegrate quickly in the gastrointestinal tract to allow a fast uptake into the body.

Immediate-release dosage forms usually release (dissolve or disperse) the drug in a single action following a first-order kinetics profile. This means the drug is released initially very quickly and then passes through the mucosal membrane into the body, reaching the highest plasma level (termed Cmax) in a comparatively short time (termed tmax). Uptake through the mucosal membranes may be due to passive diffusion or by receptor-mediated active transport mechanisms (see section on modified release). Once taken up into the body the drug is distributed throughout the body and elimination of the drug by metabolism and excretion occurs. [7,8]

The currently employed CR technologies for oral drug delivery are diffusion- controlled systems; solvent activated systems and chemically controlled systems. Diffusion controlled systems include monolithic and reservoir devices in which diffusion of the drug is the rate limiting step through a polymer matrix or a polymeric membrane respectively. Solvent activated systems may be either osmotically controlled or controlled by polymer swelling. Chemically controlled systems release drugs via polymeric degradation (surface or bulk matrix erosion) or cleavage of drug from polymer chain. It is worth mentioning here that so called programmed release (tailored release) profile of a final CR product is rarely the outcome of a single pharmaceutical principle. Depending upon physicochemical properties of the drug in question and desired therapeutic objectives different formulations and CR principles may be proportionally combined within the same dosage form. This task appears to be simpler when realized in terms of appropriate selection of polymers and excipients that incorporate different principles.

Site specific oral drug delivery requires special placement of drug delivery device at a desired site within the GI tract. Although it is virtually possible to localize a device within each part of GI tract, the attainment of site specific delivery in the oral cavity and the rectum is relatively easier than in the stomach and the small and large intestines. The later requires consideration of both longitudinal and transverse aspects of GI constraints. Some of the potential CR and site specific DDSs will be described.

MATERIALS AND METHOD:

Clopidogrel bisulphate gift sample obtained from MSN Pharmachem pvt.ltd., Microcrystalline cellulose PH102 from Weiming pharmaceutical Mfg.co.ltd, Mannitol DC Grade from SPI Pharma, and L-Hydroxy propyl cellulose (LH-11,21) from Shin-Etsc chemicals

Preformulation Studies

Preformulation may be described as a stage of development during which the physicochemical and biopharmaceutical properties of a drug substance are characterized. It is important part of the drug development process. The information relating to drug development acquired during this phase is used for making critical decisions in subsequent stages of development. A wide variety of information must be generated to develop formulations rationally. Characterization of the drug is a very important step at the preformulation phase of phase of product development followed by studying the properties of the excipients and their compatibility.

Organoleptic Properties

The drug sample was viewed visually and viewed under the compound microscope for the determination of its color using black and white backgrounds and the nature of the drug sample. Then the results were compared with the official books.

Solubility
The solubility of the drug sample was carried out in different solvents (aqueous and organic) according to the United States Pharmacopoeia. The results are then compared with those given in the United States Pharmacopoeia. Solubility can be determined by placing the drug in a vial along with the solvent. The tightly closed vial is then agitated at constant temperature and the amount of drug in solution is determined periodically by assay of filtrate sample of the supernatant. Solubility of drug substance was performed in purified water, 0.1N HCl, Acetate buffer pH4.5 and Phosphate buffer pH6.8

Water Content:
Methanol was transferred to the titration vessel and titrated with Karl fisher reagent to the electrometric end point to consume any more moisture content that may be present. 300-500mg of drug was transferred to the titration vessel and titrated with the Karl fisher reagent to the electrometric end point. Water content present in the sample was calculated by the formulae

Calculation:

$$\text{Water (\%)} = \frac{S \times F \times 100}{W}$$

Where, **S** = volume in ml of reagent consumed in the second titration

F = water equivalent factor of KF reagent

W = weight of sample taken in mg

FLOW PROPERTIES:
Angle Of Repose:
It is a direct measure of flow property of powders. It is the maximum angle that can be obtained between the free standing surface of a powder heap and the horizontal.

Angle of repose was determined using funnel to pour the powder on the surface from a fixed height of 2cm. Circumference was drawn with a pencil on the graph paper and the radius of base of a pile was measured at 5 different points and average was taken for calculating angle of repose using following formula:

$$\text{Angle of repose } (\phi) = \text{Tan}^{-1}(H/R)$$

Where, H= height of a pile (2cm)

R= radius of pile base

Bulk Density
It is ratio of mass of powder and its bulk volume determined by measuring the volume of known mass of the powder sample that has been passed through the screen into graduating cylinder. Bulk density was determined according to USP method I. The powder sample under test was screened through sieve no.18 and 10g of pure drug was weighed accurately and filled in a 100ml graduated cylinder and the powder was levelled and unsettled volume (V_O) was noted. Bulk density was calculated in g/ml by a formula:

$$Db = M / V_O$$

Where M= mass of the powder

VO= Unsettled apparent volume

Tapped Density
Tapped density was determined by USP method II. The powder sample under test was screened through sieve no.18 and 10g of pure drug was weighed accurately and filled in a 100ml graduated cylinder of tap density tester (Electrolab ETD 1020). The tapping of the cylinder was carried out using tapped density tester at a normal rate of 250 drops per minute for 500 times initially and the initial tapped volume (Va) was noted. Tapping was proceeded further for 750 times and volume was noted. The difference between two tapping volumes was calculated. Tapping was continued for additional 1250 tap if the difference is more than 2%. This was continued in increments of 1250 taps until difference between volumes of subsequent tapping was less than 2%. This volume was noted as, the final tapped volume (V_O). The tapped density was calculated in g/ml by a formula:

$$Db = M / V_O$$

Where M= mass of the powder

V_O= Final tapped volume

Compressibility Index and Hausner's Ratio:
Compressibility index and Hausner's ratio are measures of the propensity of a powder to be compressed and provide relative importance of interparticulate interactions. The free flowing powder has less interparticulate interactions and bulk and tapped density difference is close when compared to poorer flowing materials.

Carr's index i.e., %compressibility indicates the flow property and packing ability of the tablet. It was determined by measuring both bulk and tapped density of the powder. Compressibility index was calculated by the following equation:

CI (%) = [(Dt-Db)/Dt] × 100

Where, Dt= tapped density

Db = bulk density

Hausner's ratio was calculated using the formula

Hausner's ratio= Dt / Db

Dt = tapped density

Db = bulk density

Drug-Excipient Compatibility Studies:
The objective of this study was to determine the interactions of Clopidogrel bisulfate with excipients in the formulation. FTIR studies were done to verify if there was any interaction between the pure drug and excipients employed. The various FTIR graphs of pure drug, physical mixture and placebo are mixed and the blend was formulated into IR pellet and scanned.

Manufacturing Process:

STEP I: SIFTING

All raw materials are weighed according to formula and sifted through the sieve #30

STEP II: PREBLENDING AND FINAL BLENDING
Preblending: All sifted materials except Cutina HRPH are placed in octagonal blender and blended for 15min

Final blending: All sifted materials, Cutina HRPH loaded into the octagonal blender and blended for 5min. Samples were taken from at least three places from the blender and the samples were sent to QC for in process analysis.
After the QC approval the samples were subjected to tablet making

STEP III: TABLET MAKING
The blended material was compressed into tablets using rotary die apparatus as per SOP

STEP IV: FILM COATING
Tablets were coated with the coating solution of Opadry II pink

Evaluation of Tablets
Weight Variation Test:
This is an in process quality control test to be checked frequently (every half an hour). Corrections were made during the compression of tablets. Any variation in the weight of tablets (for any reason) leads to either under medication or overdose. So, every tablet in each batch should have a uniform weigh. The weight variation test was performed as per USP. Twenty tablets were selected at random and their average weight was determined using an electronic balance. The tablets were weighed individually and compared with average weight.

Hardness Test:
Hardness (diametric crushing strength) is a force required to break the tablet across the diameter. The hardness of a tablet is an indication of its strength. The tablet should be stable to mechanical stress during handling and transportation. The degree of hardness varies with the different manufacturers and with the different types of tablets. The permissible limit for hardness is 4-12 kg/cm2. The hardness of the tablets was determined by digital hardness tester. Ten individual tablets from each trial were taken and measured individually at frequent intervals.

Thickness
The thickness of the tablets was determined by digital micrometer. Ten individual tablets from each trial were taken and measured individually at frequent intervals.

Friability Test:
Friability of the tablets was determined by using Roche Friabilator (Electrolab, India).
This device consists of a plastic chamber that is set to revolve around 25 rpm for 4 minutes dropping the tablets at a distance of 6 inches with each revolution. Friability was determined by taking 20 tablets. Tablets were weighed and placed in a Friabilator, after the given specified time (4min at 25rpm) tablets were again weighed and the friability (F %) is given by the formula

$$F\ \% = (1-W_0/W) \times 100$$

Where, W_0 is weight of the tablets before the test and W is the weight of the tablets after test.

Disintegration Test:
Disintegration time was measured using USP disintegration test apparatus (ED2L, Electrolab, India by using 900ml distilled water at room temperature (37±20°C)

Dissolution Test parameters
Medium: pH 2.0 HCl, pH 4.5 sodium acetate buffer, Ph 6.8 phosphate buffer
Apparatus: paddle type
Speed: 50 rpm

Temperature: 37±0.5°C
Run time: 30 min
Dissolution Test Procedure:
6 tablets were placed in each of 6 dissolution flasks containing 900 ml of pH 2.0 HCl maintained at 37±0.5°C. The apparatus was run for 30 minutes. A suitable volume of sample was withdrawn at regular intervals of time and filtered through 0.45 µm membrane filter. The absorbance of the sample preparations were measured at 249 nm, using pH 2.0 HCl as blank

Stability Studies
The design of the formal stability studies for the drug product was based on the knowledge of the behavior and properties of the drug substance and formal stability studies on the drug substance. Specification which is list of tests, reference to the analytical procedures and proposed acceptance criteria, including the concept of different acceptable criteria for release and shelf life specifications, is addressed in ICH (Temperature: 40±2°C Relative humidity: 75±5% for 3 months)

Release Kinetics
The mathematical models are used to evaluate the kinetics and mechanism of drug release from the tablets. The model that best fits the release data is selected based on the correlation coefficient (r) value in various models. The model that gives high 'r' value is considered as the best fit of the release data.
Mathematical models are
1) Zero order release model
2) First order release model
3) Hixson-crowell release model
4) Higuchi release model
5) Korsmeyer – peppas release model

Zero Order Release Equation
The equation for zero order release is

$$Qt = Q0 + K0\,t$$

Where
Q0 = initial amount of drug
Qt = cumulative amount of drug release at time "t"
K0 = zero order release constant
t = time in hours It describes the systems where the drug release rate is independent of its concentration of the dissolved substance.
A graph is plotted between the time taken on x-axis and the cumulative percentage of drug release on y-axis and it gives a straight line.

First Order Release Equation
The first order release equation is
Log Qt = Log Q0+ Kt /2.303
where Q0 = initial amount of drug
Qt = cumulative amount of drug release at time "t"
K = first order release constant
t = time in hours Here, the drug release rate depends on its concentration
A graph is plotted between the time taken on x-axis and the log cumulative percentage of drug remaining to be released on y-axis and it gives a straight line.

Hixson - Crowell Release Equation
The Hixson - Crowell release equation is

$$\sqrt[3]{Q_0} - \sqrt[3]{Q_t} = K_{HC} \cdot t$$

Where
Q0 = Initial amount of drug
Qt = Cumulative amount of drug release at time "t"
KHC = Hixson Crowell release constant t = Time in hours. It describes the drug releases by dissolution and with the changes in surface area and diameter of the particles or tablets.
34 A linear plot of the cube root of the initial concentration minus the cube root of percent remaining versus time in hours for the dissolution data in accordance with the Hixson-crowell equation

Higuchi Release Equation
The Higuchi release equation is
Q=KHt1/2
Where
Q = cumulative amount of drug release at time "t"
KH = Higuchi constant t = time in hours
The Higuchi equation suggests that the drug release by diffusion.
A graph is plotted between the square root of time taken on x-axis and the cummulative percentage of drug release on y-axis and it gives a straight line.

Korsmeyer-Peppas Equation
Korsmeyer – peppas equation is
F = (Mt /M) = Kmtn
Where
F = Fraction of drug released at time't'
Mt = Amount of drug released at time't'
M = Total amount of drug in dosage form
Km = Kinetic constant
n = Diffusion or release exponent
t = Time in hours
'n' is estimated from linear regression of log

(Mt/M) versus log t If n = 0.45 indicates fickian diffusion 0.45<n<0.89 indicates anomalous diffusion or non-fickian diffusion.

If n = 0.89 and above indicates case-2 relaxation or super case transport-2. Anomalous diffusion or non-

fickian diffusion refers to combination of both diffusion and erosion controlled rate release. Case-2 relaxation or super case transport-2 refers to the erosion of the polymeric chain

A graph is plotted between the log time taken on x-axis and the log cummulative percentage of drug release on y-axis and it gives a straight line

RESULTS AND DISCUSSION:

Preformulation Parameters

Physical characterization

Table 1: Physical characterization of optimized formulation

SL.NO	DESCRIPTION	RESULT
1	Appearance	White to off-white powder.
2	Odor	Odorless
3	Solubility	Practically insoluble in water, freely soluble at pH 1, also dissolves freely in methanol, dissolves sparingly in methylene chloride, and is practically insoluble in ethyl ether.
4	Loss on drying	0.33% w/w
5	Residue on ignition	0.08%w/w
6	Identification by FTIR and HPLC	Complies

DRUG EXCIPIENT COMPATIBILITY STUDIES

DRUG- EXCIPIENT STUDIES BY FTIR

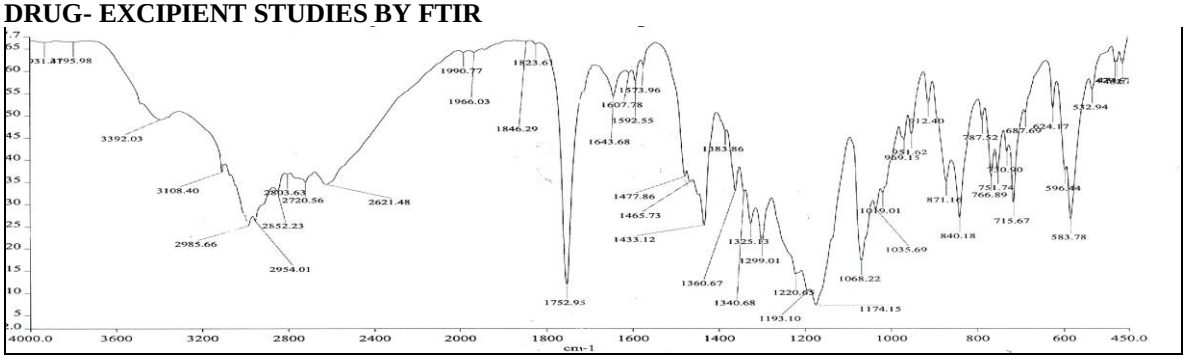

Fig.1: FTIR spectra of Clopidogrel bisulfate standard

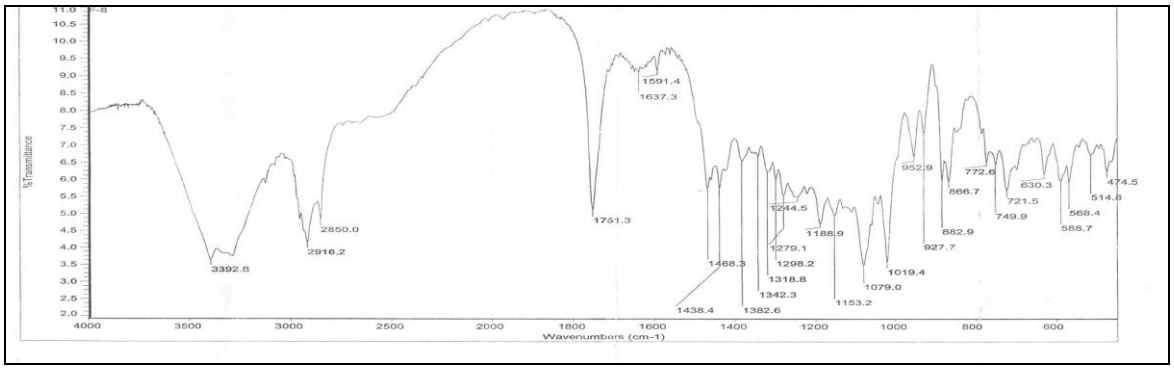

Fig.2: FTIR spectra of F8 formulation

INFERENCE: From all the FTIR spectra I conclude that there are no incompatibilities observed between drug and excipients

Results of Flow Properties

Table 2: Results of flow properties of granules

Sl. no	Formulation trials	Angle of repose (ø)	Bulk density	Tapped density	Compressibility index	Hausne's ratio
1	F-1	38.23	0.596	0.785	24.07	1.31
2	F-2	25.51	0.581	0.714	18.60	1.22
3	F-3	37.12	0.654	0.802	18.45	1.22
4	F-4	36.34	0.694	0.834	16.67	1.2
5	F-5	42.13	0.480	0.625	23.07	1.30
6	F-6	29.23	0.519	0.732	29.09	1.443
7	F-7	26.48	0.583	0.745	21.74	1.277
8	F-8	28.81	0.582	0.714	18.60	1.22
9	F-9	35.13	0.510	0.641	20.40	1.25
10	F-10	25.31	0.500	0.735	32	1.47
11	F-11	25.65	0.535	0.756	19.8	1.47
12	F-12	26.79	0.514	0.654	20.45	1.23

Post Compression Parameters

Table 3: Results of post compression parameters

Sl.no	Formulation	Average weight (mg)	Thickness	Hardness
1	**INNOVATOR**	247	3.50±0.04	9.8±0.14
2	F-1	246.8	3.63±0.099	4.2±0.31
3	F-2	246.90	3.62±O.O16	5.3±0.42
4	F-3	247.50	3.43±0.035	10.44±0.49
5	F-4	247.80	3.46±0.024	2.75±0.51
6	F-5	246.70	3.48±0.029	6.09±0.24
7	F-6	246.8.55	3.47±0.053	5.46±0.32
8	F-7	246.90	3.53±0.022	9.45±0.59
9	F-8	247.12	3.5±0.022	2.9±0.47
10	F-9	245.80	3.55±0.019	9.6±0.35
11	F-10	245.32	3.54±0.016	7.1±0.27
12	F-11	246.9	3.53±0.02	3.5±0.13
13	F-12	247.8	3.55±0.016	4.0±0.56

Table 4: Results of post compression parameters

Sl.no	Formulation	Disintegration	Friability	Assay
1	**INNOVATOR**	11.17	0.15±0.56	98.8±0.54
2	F-1	40.16	0.153±0.56	96.4±0.79
3	F-2	3.02	0.106±0.76	97.3±0.76
4	F-3	8.5	0.377±0.65	94.1±0.56
5	F-4	14.55	0.24±0.54	98.5±0.76
6	F-5	11.5	0.17±0.86	97.4±0.87
7	F-6	11.2	0.28±0.76	90.3±0.79
8	F-7	12	0.23±0.45	92.4±0.67
9	F-8	10	0.5±0.56	99.8±0.56
10	F-9	5.5	0.06±0.59	98.5±0.98
11	F-10	12	0.16±0.57	98.2±0.76
12	F-11	13.02	0.4±0.45	98.3±0.45
13	F-12	13.53	0.5±0.79	97.4±0.76

Dissolution Results

IN P^H 2.0 HCL BUFFER

Table 5: invitro drug release of formulation trial batches

Sl.NO	TIME	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
1.	0	0	0	0	0	0	0	0	0	0	0	0	0
2.	10	60.6	61	63.7	54.5	59.3	61	62	62.7	54.1	54.5	48.3	53.1
3.	15	80.2	74	74	72.3	74.3	74	73.6	78.8	77.8	81.2	75.7	74
4.	20	82.9	82.9	86	88.7	88.7	92.1	86	90	85.3	88	88	88
5.	30	95.6	96.6	94.5	91.5	91.5	96.6	91.8	99	90.3	90.4	90.8	98.3

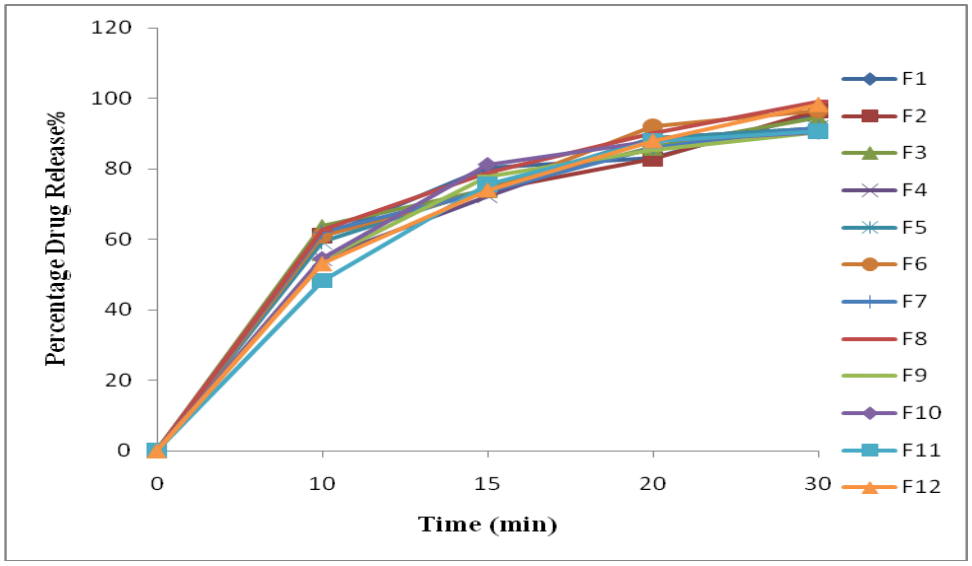

Fig.3: Comparison of invitro % drug release in pH2.0 HCL buffer with the innovator

***In-vitro* Drug Release Of Optimised Batch**

Table 6: Invitro drug release of optimized formulation

Sl .NO	TIME	F8
1.	0	0
2.	10	62.7
3.	15	78.8
4.	20	90
5.	30	99

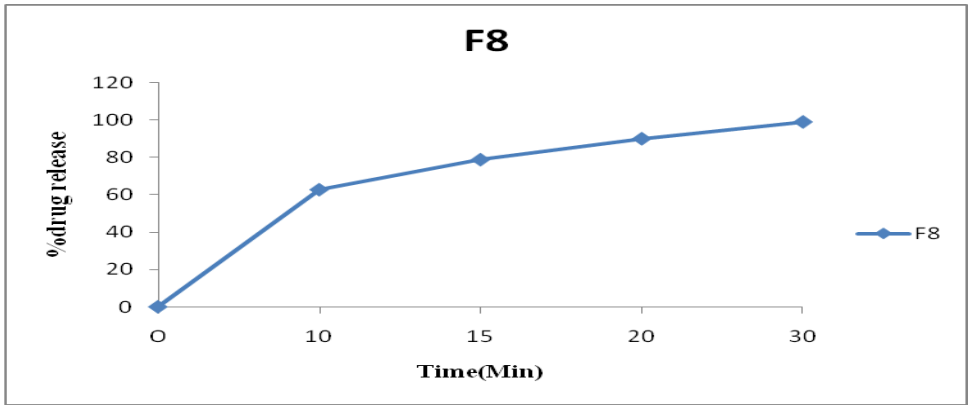

Fig.4: Invitro % drug release of optimized formulation in pH2.0 HCL buffer

Comparitive *In-vitro* Drug Release Studies Of F8 Formulation with the Innovator

Table 7: Comparison of F8 formulation with the innovator

TIME	F8	INNOVATOR
0	0	0
10	62.7	54
15	78.8	74
20	90	88
30	99	98.3

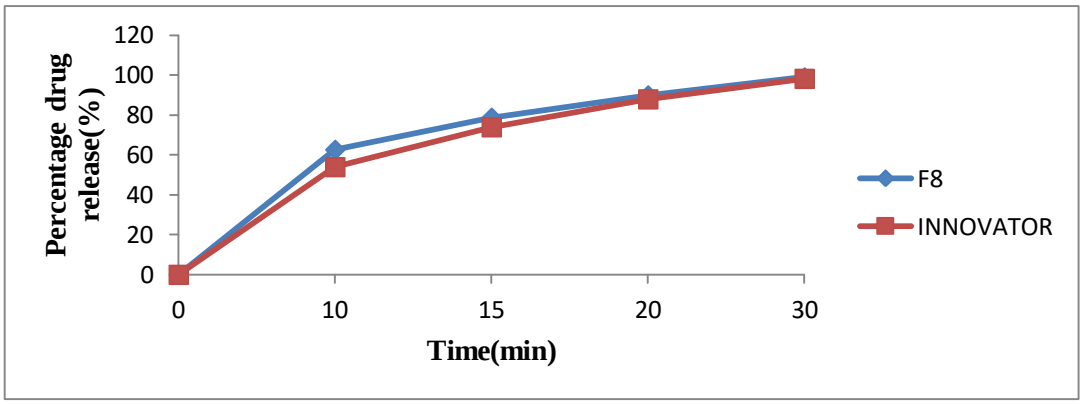

Fig.5: Comparison of F8 formulation with the innovator

FIRST ORDER KINETICS

Table 8: First order release kinetics

Time (min)	% drug release	% drug remained	Cummulative% drug remained	Log cummulative % drug remained
0	0	100	62.7	1.797267541
10	62.7	37.3	15.6	1.193124598
15	78.8	21.7	11.7	1.068185862
20	90	10	9	0.954242509
30	99	1		

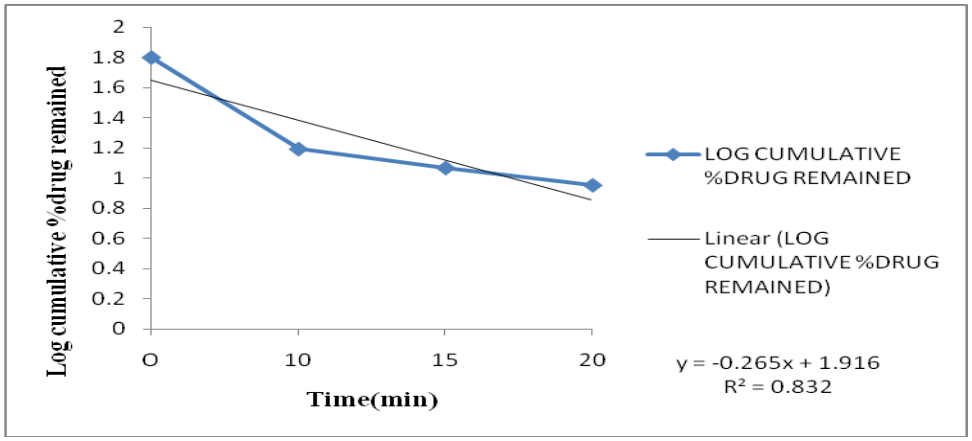

Fig.6: First order kinetics

SIMILARITY AND DIFFERENCE FACTORS

Table 9: Similarity and difference factors

N	INNOVATOR (Rt)	F-8 (Tt)	D=(Rt-Tt)	$(Rt-Tt)^2$	f_1	f_2
0	0	0	0	**0**	5.15	64.29
10	54	62.7	-8.7	75.69		
15	74	78.8	-4.8	23.04		
20	88	90	-2	4		
30	98.3	99	-0.7	0.49		

STABILITY STUDIES

Table 10: Stability studies of optimized formulation

CONDITIONS					
Sl.no	Assay(%w/w)	Initial	40c & 75% RH		
		0 Day	1 month	2month	3month
1	Optimised formulation (F8)	100.3	99.8	99.5	99.6
2.	Innovator	100	99.8	99.6	99.6

Dissolution of optimized formulation maintained for stability with pH 2.6 HCL buffer of batch F-8

Table 11: Dissolution of optimized formulation maintained for stability with pH 2.6 HCL buffer of batch F-8

Time (min)	Initial	1st month	2nd month	3rd month
0	0	0	0	0
10	62.7	62.8	62.9	62.4
15	78.8	77.9	78.3	78.7
20	90	89.6	90	91
30	99	99	98.8	98.7

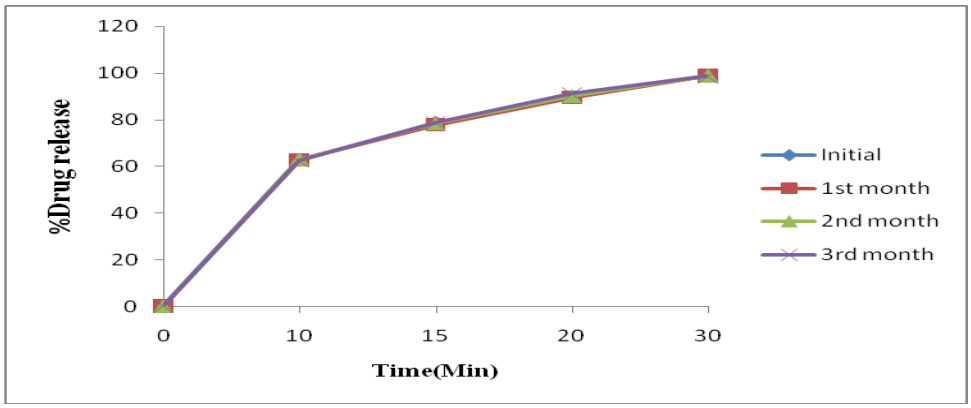

Fig.7: Dissolution profile of optimized batch for stability studies

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