FORMULATION DESIGN AND *IN-VITRO* EVALUATION OF CONTROLLED RELEASE CELECOXIB TABLET USING DIFFERENT POLYMER

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Abstract:

:The objective of present investigation study was carried out to modulate the release rate and reduce the dosage frequency of celecoxib, because frequency of doses causes ulcer in stomach, bleeding, holes in the stomach or intestine. When doses increase consumption of additives also increase. To minimize the side effect and for getting prolonged effect the study was carried out. In this study hydrophilic and hydrophobic polymers are used for making this formulation. Since celecoxib is freely soluble in alkaline aqueous solution hydrophilic polymers alone cannot retard the rate of release. So hydrophobic polymer Eudragit RL 100 is selected. HPMC used as a hydrophilic polymer. This controlled release tablets were prepared by direct compression technique. The pre-compressed powder blend was evaluated for various parameters like angle of repose, compressibility index and Hausner's ratio. So all the parameters were suitable for direct compression. Then the prepared matrix tablets were evaluated for hardness, thickness, friability, weight variation, drug content and invitro release. Dissolution studies revealed that optimized formulation (F5), release the drug up to 24 hours in controlled manner.

Keywords: Controlled Release Tablets, Eudragit RL 100, HPMC, Celecoxib.

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Introduction:

When tablets with an immediate release or conventional release reach their maximum effective concentration, they begin to be removed from the body with a rapid initiation of action. Celecoxib controlled release pills are frequently recommended to treat chronic, severe neurological pain brought on by a few long-lasting disorders. Tablets with controlled release are utilised for actions that last a long time but have little therapeutic benefit. To achieve continuous release of the API, they are formulated with natural high intensity polymer. A loading dosage and a maintenance dose are included in the formulation of controlled release tablets .The maintenance dosage keeps the level of the medication in the plasma for the MEC while the loading dose offers an instantaneous plasma concentration of the API to have an immediate impact [1-5]. COX-2 inhibitor and non-steroidal anti-inflammatory medication, celecoxib is primarily used to treat inflammation. Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, low back pain, acute back pain, and gout are all conditions it is used to treat. Although celecoxib is widely soluble in alkaline aqueous solution, it is insoluble in water. Usually, the medication enters the intestine after two hours. Along with hydrophilic polymer, hydrophobic polymer is added to prevent the rapid release of celecoxib in the colon. It lowers the production of prostaglandin from arachidonic acid and specifically inhibits 2-cyclo oxygenase. One of the sustained release polymers, Eudragit RL 100, provides release for up to 24 hours. Due to its insoluble nature, high permeability, and pH independence [6-10].

Materials and methods:

8 Stage dissolution apparatus Electrolab ,SPCOP , Otur ;Tableting machine ,(Mini Press - π MT)Rimek 6 Stations ,SPCOP , Otur ;U.V / Visible spectrophotometer Agilant ,SPCOP , Otur ;Analytical balance Contech, SPCOP , Otur ;Friabilator Labline ,SPCOP , Otur ;Hardness tester Labline ,SPCOP , Otur ;Tray dryer Labline ,SPCOP , Otur ;Tapped density tester Electrolab , SPCOP , Otur . Celecoxib Niksan Pharmaceutical pvt. limited, Ankleshwar ,Gujrat, India.; Avicel 101, SPCOP , Otur HPMC K4, SPCOP , Otur; Eudragit L-100 SPCOP , Otur; Talc SPCOP , Otur ;.Aerosil, SPCOP , Otur

Method of preparation of tablets

Controlled release matrix tablets of celecoxib were prepared by direct compression methods using 6 no. station . The active ingredients and additives like microcrystalline cellulose, HPMC, Eudragit RL100 were passed through sieve no.80 Finally aerosol and talc were added to the blend and mixed for 10 minutes. Different trials were made with hydrophilic polymer (HPMC) alone and combination of hydrophilic and hydrophobic polymers [11-13]

Composition of Matrix Tablet

INGREDIENTS	**FORMULATION CODE**				
	F1	F2	F3	F4	F5
	HPMC:EUDRAGIT RATIO				
	0:3:0	0:6:0	1:0:3	1:0:6	1:1
Celecoxib	120	120	120	120	120
HPMC	25	50	75	75	75
Eudragit RL-100	-	-	25	50	25
MCC	150	125	75	50	28
Talc	3	3	3	3	3
Aerosil	2	2	2	2	2
Average wt.	300	300	300	300	300

Table No 1. Composition of Matrix Tablet

Characteristics of tablet formulation

Weight fluctuation, hardness, disintegration, friability, content uniformity of dose, and dissolving profile were the characteristics of the tablets. According to the United States Pharmacopoeia's (U.S.P.) 2006 recommendations, the average weight was measured over 20 units. Over the course of 10 tablets, the hardness was measured in a Hardness tester Labline ,SPCOP , Otur .The friability of each formulation was examined in a Roche Friabilator across a sample of 20 tablets, with a maximum loss of 2% of original weight serving as the acceptance criterion (U.S.P. 2006). U.V / Visible spectrophotometer Agilant ,SPCOP , Otur was used to analyse sample data in order to estimate the dissolution profile. To ensure that the formulation met USP standards for quality, celecoxib controlled release tablets underwent

evaluation.2 tablets were examined for weight changes, including average and individual weight variations, thickness, hardness, drug release in vitro and test. Individual and average weight variations were monitored using a Single Pan Electronic Balance. The Roche Friabilator was used to examine the friability, which was limited to NMT 2% in accordance with USP. Utilising Electrolab's Dissolution Apparatus, dissolution was carried out [14-20]

Pre formulation study

Preformulation investigations evaluated a medicinal substance's precise physical and chemical properties both by itself and in combination with an excipient. Particle size distributions of the polymer powders were measured. Particle shape was examined using a microscope. Using a tap densiometer and determining the Hausner ratio, flow characteristics were evaluated.

For each batch of powder blends the following test were carried out as per I.P official methods.

Angle Of Repose: API was weighed and, using funnel-type and open-ended cylindrical methods, measure the pile's height and radius by passing granules through it.

Bulk Density: The API must be weighed first, and then it must be transferred without tapping into a 100-ml measuring cylinder. The amount of space the API consumed was measured. Formula was applied to measure bulk density.

Tapped density: The API quantity before adding it to a graduated cylinder weighed. The space used by the API was noted out . On an Electro Lab USP II tap density tester, the cylinder was then subjected to 500, 750, and 1250 taps. According to USP, the mixture received 500 taps. Additional 750 taps were added to the volume of calculated percentage.

Compressibility index: API was weighed and transferred it to a 100 ml graduated cylinder, and tapped it 500, 750, and 1250 times on an Electro Lab tap density tester. The distance between any two taps should be less than 2%.

Hausner's ratio: This gauge of a drug's frictional resistance, whose ideal range should be 1.2-1.5, is calculated from the difference between tapped density and bulk density.

Evaluation Studies :

For each formulation weight variation, hardness, thickness, drug content , friability were estimated as per I.P official methods

Swelling studies:

Matrix tablets were weighed and placed in metallic baskets. Baskets were immersed in 900 ml phosphate buffer of pH 7.4 and rotated at 75 rpm at 37 0.5°C (USP XXIV basket method). After specified time the tablets were removed lightly blotted with help of tissue paper to remove excess water and weighed out again.

Short term stability studies:

The stability study was conducted for F5 optimized formulation batch. The tablets were packed and kept for 1 months at 4°C, 40°C/ 75% and 60°C/ 80% RH in a Stability chamber. At the time interval of 15 days tablets were withdrawn and evaluated for physical properties like hardness, diameter, friability, weight variation and content uniformity. Invitro drug release and assay were also carried out [21-23].

Mechanism of drug release:

mechanism of drug release was found out by, fitting data in Korsemeyer-Peppar model.

$M_t/M_\alpha = Kt^n$

M_t/M_α =fraction of drug released at time't'

K=rate constant

n=it is used to characterize different release mechanism

Result and discussion:

In controlled release matrix tablets, hydrophilic polymer alone cannot give better results. Hence the present study was done with hydrophobic polymers like Eudragit RL 100 and resin gum, incorporated in hydrophilic matrix. F1 and F2 trials showed that hydrophilic polymer alone cannot give sustained effect for period of 24 hours . In next two trials addition of Eudragit RL 100 acts as a release retardant polymer, because of its hydrophobic nature and Eudragit presence on the surface of tablets so the rate of release for F3 and F4 was extended up to 12 hours only . But F5 formulation dissolution studies revealed that both HPMC and Eudragit RL100 are suitable candidates. For making optimized 24 hours Controlled release celcoxib tablet [22].

Procedure for Calibration Study :

The medication (Celecoxib) was calibrated using 0.1N HCL solution first, which followed by 6.8 pH of phosphate buffer 1. The fourth batch of

continuous calibration, which occurred after the first three batches, had an accurate regression factor of 0.999.

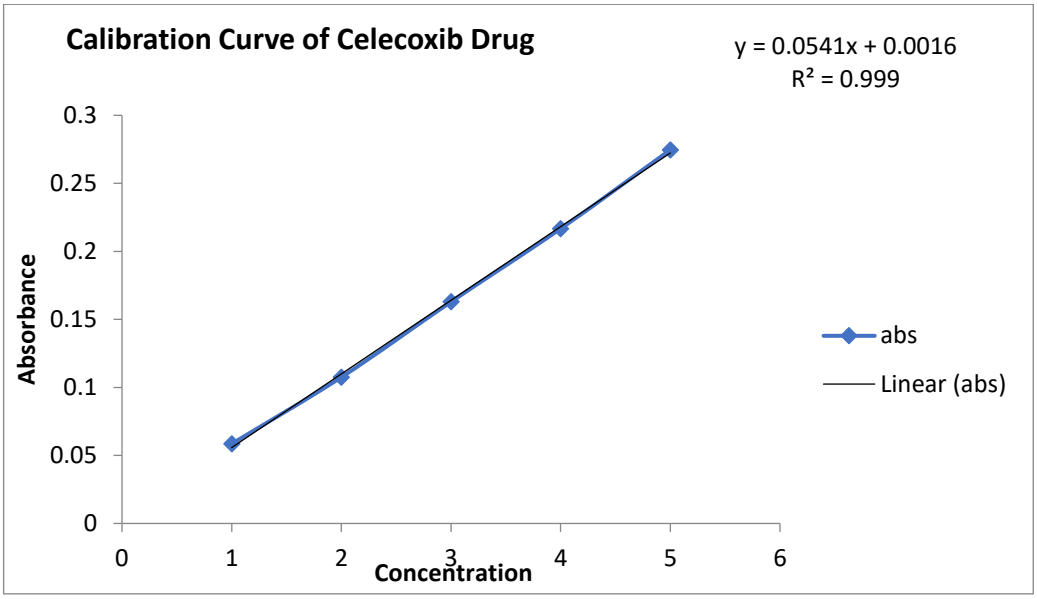

Fig. No.1 Calibration Curve of Celecoxib Drug

Procedure for drug and excipient incompatibility Study (FTIR) :
Excipients were combined with the medication celecoxib in a variety of ratios. Aliquots of these mixtures as well as the drug were stored in open 5mL glass vials which are exposed to 40°C and 75% relative humidity for one month period. At intervals of two weeks and four weeks, samples were removed for conduct physical observations and analysis .Following are the exposure of the drug and excipient

1. CELECOXIB:

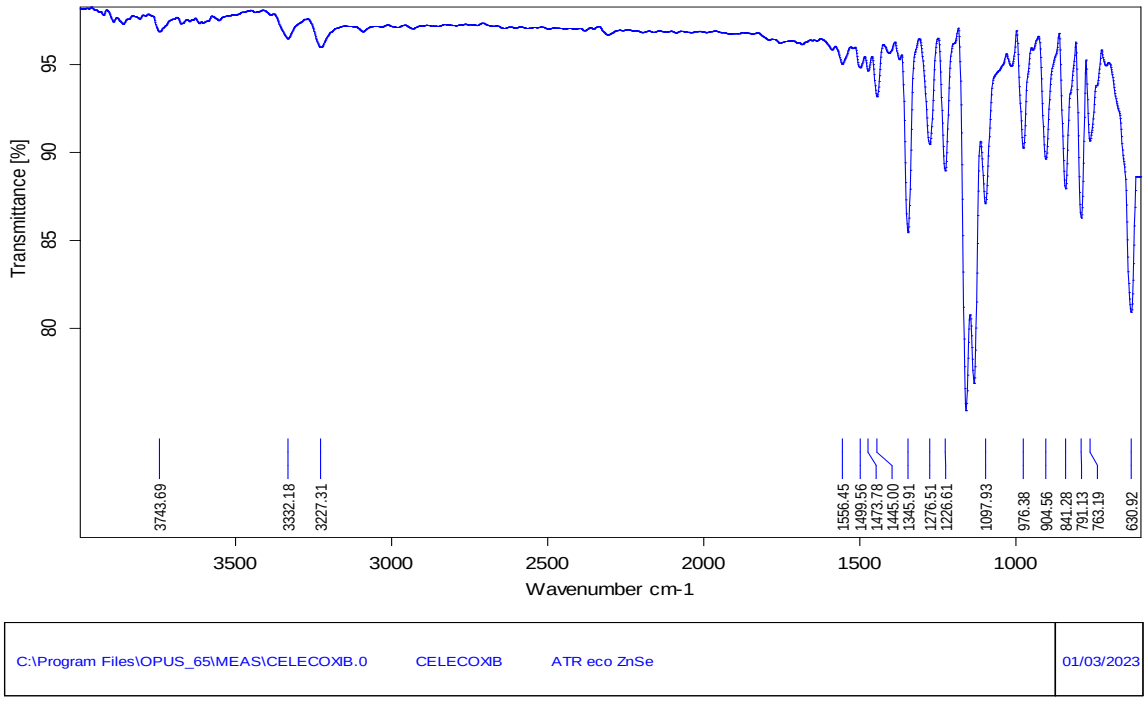

Fig. No. 2 FTIR Spectrum Of

2. CELECOXIB +HPMC:

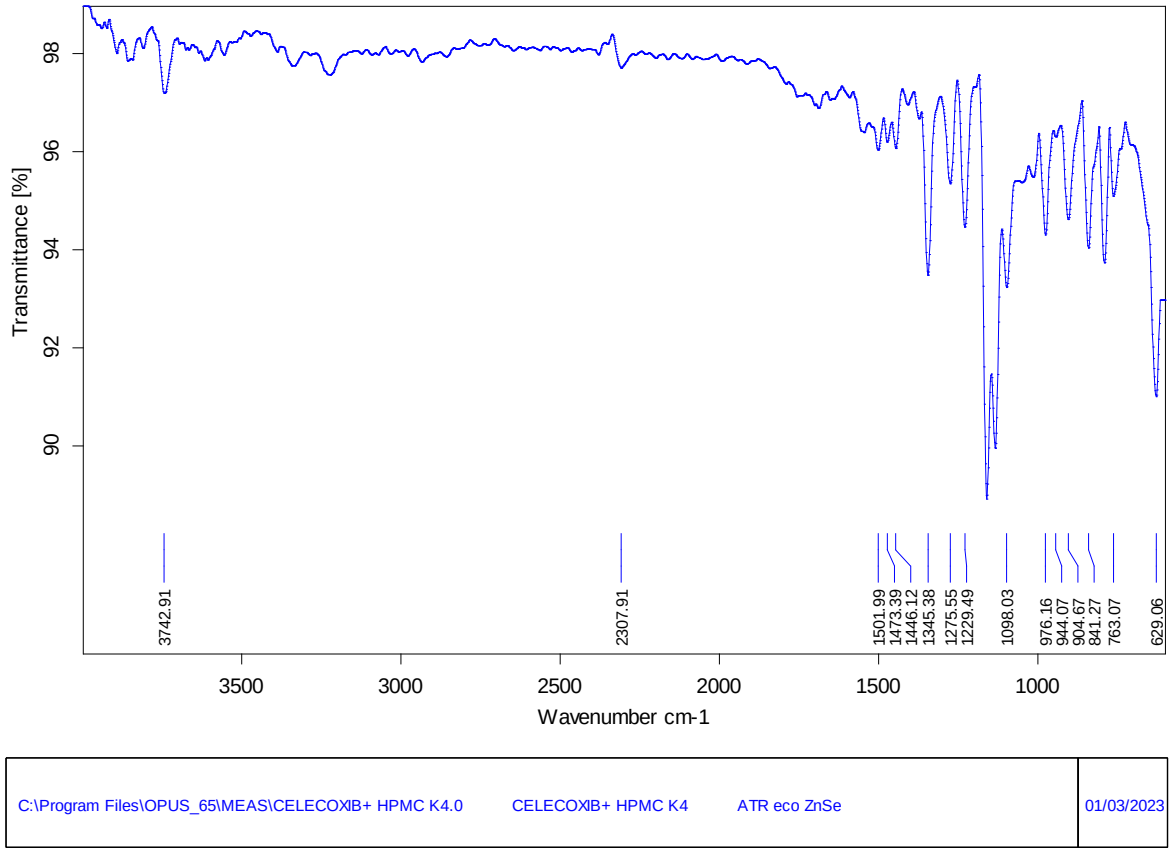

Fig. No.3 FTIR Spectrum Of Celecoxib + HPMC

3. CELECOXIB +EUDRAGIT:

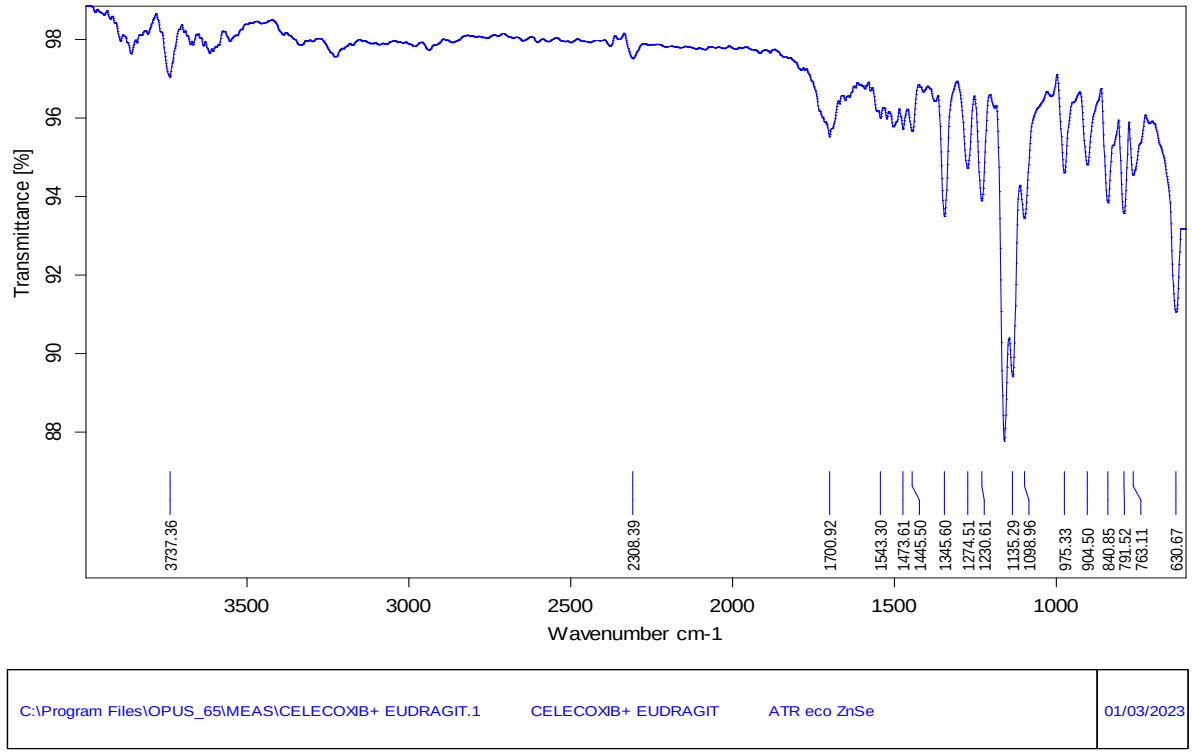

Fig. No.4 FTIR Spectrum Of Celecoxib + HPMC

4. CELECOXIB OVERPLAY:

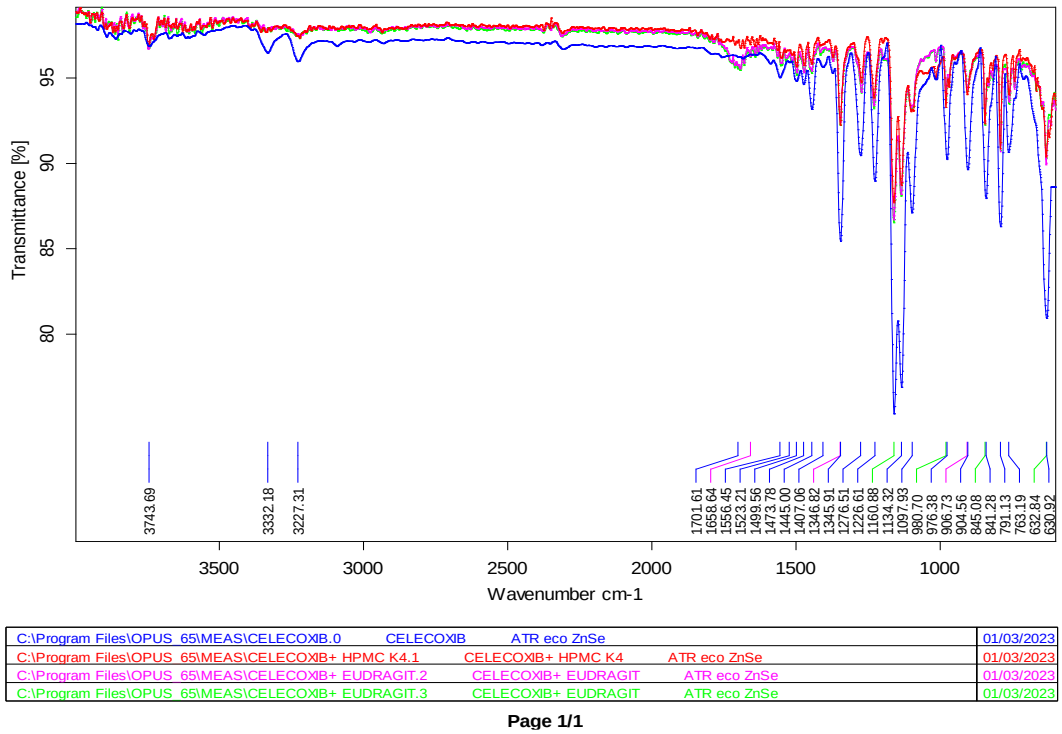

Fig. No. 5 Celecoxib overplay

Evaluation Of Precompression Parameters :

Batch	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle Of Repose
F1	0.29 ± 0.4	0.31 ± 0.33	6.45 ± 0.39	1.06 ± 0.18	17°48 ± 0.58
F2	0.29 ± 0.2	0.320 ± 0.16	9.37 ± 0.15	1.10 ± 0.58	19°79 ± 0.27
F3	0.29 ± 0.3	0.33 ± 0.42	12.12 ± 0.41	1.17 ± 0.39	18°77 ± 0.50
F4	0.28 ± 0.5	0.33 ± 0.18	15.15 ± 0.35	1.17 ± 0.13	15°1 ± 0.44
F5	0.30 ± 0.4	0.34 ± 0.27	11.76 ± 0.32	1.13 ± 0.61	16°69 ± 0.12

Table No. 2 Evaluation Of Powder Blend

Evaluation Of Postcompression Parameters :

Batch no.	Average Weight (mg)	Hardness (Kg)	Friability (%)	Percentage drug Content (%)
F1	324±1.62	5.2±0.05	0.811	99.65
F2	325±2.53	5.5±0.03	0.652	99.95
F3	328±2.75	5.6±0.02	0.725	100.4
F4	336±2.98	5.1±0.04	0.845	100.1
F5	327±1.28	5.2±0.03	0.832	100.2

Table No.3 Physical Parameters Of Tablet

Dissolution study:

Dissolution profiles of celecoxib tablets were determined by using the USP 24 Method II with paddle speed at 50 rpm. Dissolution study was performed in 900 ml 0.1N HCl maintained at 37± 0.5ºC. Five milliliters samples were withdrawn at specified time intervals. The volume of dissolution fluid was adjusted to 900 ml, by replacing each 5 ml volume aliquot withdrawn with 5 ml of 0.1N HCl, prewarmed at 37± 0.5ºC. Samples withdrawn were filtered by Whatmann filter paper (no.41) and suitably diluted with 0.1N HCl, analyzed at 233 nm, by using an UV-Visible double beam spectrophotometer. After 2 hours dissolution was performed by using 900ml pH 7.4 phosphate buffer .Samples were withdrawn at specified intervals and diluted with buffer and analysed at 233nm using spectroscopy.[17]

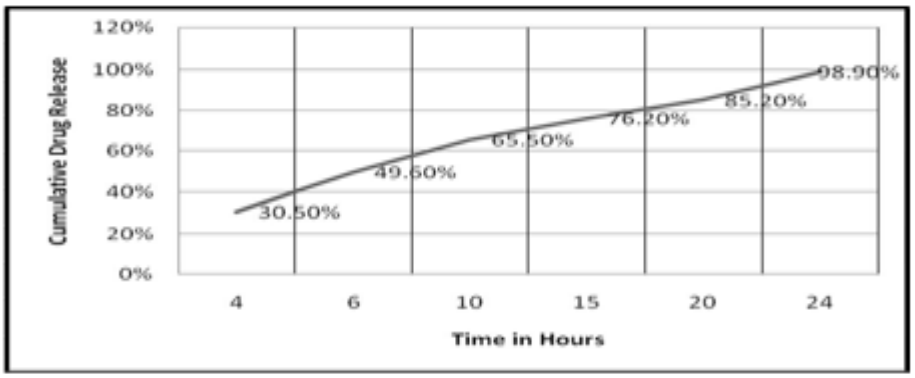

Fig. No. 6 Drug Release Study

Conclusion :

From this investigation and mentioned discussion Hydrophilic polymer alonely cannot give the controlled release effect for celecoxib , Incorporation of HPMC in Eudragit RL100 (1:1) is the best technique for getting controlled release of celecoxib for 24 hours. This F5 optimized formulation will useful for further studies in future.

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