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Designing and Evaluation of Dual Release Bi-Layer of Aceclofenac Optimized By SSG and Combination Of HPMC K 4M and PVP- K30

Popin Kumar*, Tulsi Bisht, Poornima Belwal
Gyani Inder Singh Institute of Professional Studies, opp. Malsi deer park, Dehradun,Uttarakhand,

Abstract: *The aim of the present investigation to development and evaluation of bi-layer drug delivery system of aceclofenac to produce rapid and continuous action throughout the treatment to increase the patient compliance. Drugs with short half life cannot maintain the plasma drug concentration at the therapeutic levels for a longer period of time. So as to decrease the dosing frequency and increase the patient compliance sustained release bi-layer tablets were designed. Developed immediate release instant and rapid action and sustain release maintain the plasma drug concentration level. The physicochemical properties of the optimized bi-layered was investigated. Sodium starch glycolate and combination of HPMC K4M and PVP- K30 was incorporated bi-layer formulation to achieve the desired drug release profile. The formulation containing HPMC K4M and PVPK30 was selected as the optimized batch since it showed the best drug release profile within 6 hours as compared to the other formulations. The optimized batch was also analyzed for its morphological, physiochemical and drug release properties. Batches with combination of HPMC and PVK30 were evaluated for the % drug release. This work indicates the possible advantage in designing of sustain release medication for the long term treatment.*

Keywords: *Bi-layered tablets, Aceclofenac, SSG, HPMC K4M, PVP K30.*

I. Introduction

Oral ingestion has long been the most convenient and commonly employed route of drug delivery due to its ease administration, least aseptic constrain and flexibility in the design of the dosage form [1-2]. Pharmaceuticals products designed for oral deliveries are mainly immediate release type or conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption[3].

Introduction of bi-layer tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the Pharmaceutical technology. Bi-layer systems are widely used for the purpose of sustained release and immediate release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed [4].

By the sustained release method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. In order to overcome the drawbacks of conventional drug delivery systems, several technical advancements have led to the development of controlled drug delivery system that could revolutionize method of medication and provide a number of therapeutic benefits[5-8].In recent years, a growing interest has developed in designing drug delivery systems that include an immediate release (IR) component to extended release (ER) dosages .The addition of an IR component allows one to design delivery systems having optimal pharmacokinetic profiles and enables the combination of different drugs thereby improving patient compliance[9-10].

In certain conditions (migraine and sleeping disorders), drug treatment may be advantageous to be delivered in a bi-phasic manner rather than a single phase extended release preparation. In the first phase of drug release, the immediate release dose fraction (also called loading-dose) reaches a therapeutic drug level in the blood plasma quickly after administration, while the second extended release phase (called the maintenance-dose) provides the dose fraction, required to maintain an effective therapeutic level for a prolonged period[11-16].

Types of Bi-layer Tablets

The term bi-layered tablets containing subunits that may be either the same (homogeneous) or different (heterogeneous) [17-20].

1- Homogenous type

Bi-layer tablets are preferred when the release profiles of the drugs are different from one another. Bi-layer tablets allows for designing and modulating the dissolution and release characteristics .Bi-layer tablets are prepared with one layer of drug for immediate release while second designed to release drug ,later, either as second dose or in an extended release manner.

2- Heterogeneous type

Bi-layer tablet is suitable for sequential release of two drugs in combination, separate two Incompatible substances[21].

Fig.1.1- Homogenous Bi-layered tablets (same drug with different release pattern)

Fig: 1.2 Heterogeneous Bi-layer tablet (With different drugs)

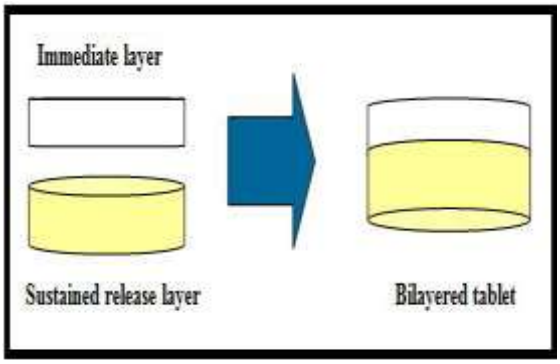


Fig: 1.1

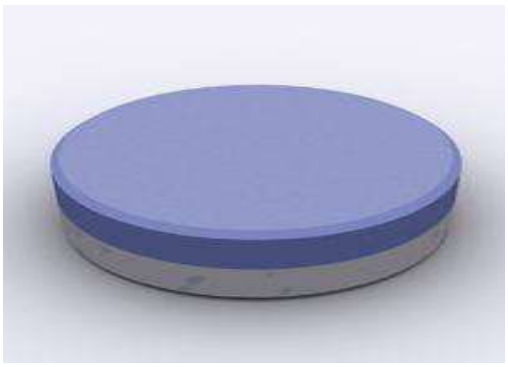


Fig: 1.2

II. Material And Method

Aceclofenac is given by macloid pharmaceuticals, HPMC Combination of HPMC K 4M, MCC was provided by GISIPS, Dehradun and Sodium starch glycolate provided by sheron biomedicine, selaqui, dehradun, Uttarakhand.

Selection criteria for the drug and polymers

Aceclofenac is a newer derivative of the diclofenac group of non-steroidal anti inflammatory drug (NSAID) that exhibits analgesic and anti-inflammatory activities. It directly blocks the prostaglandin synthesis. It has less gastrointestinal complications. It is considered to be the first-line drug in the symptomatic treatment of rheumatoid arthritis, osteoarthritis and ankylosing spondylitis [22-30]. The short biological half-life (4 h) and frequent dosing make aceclofenac an ideal candidate for sustained release dosage forms. For sustained release systems, the oral route of drug administration has, by far, received the most attention as it is natural, uncomplicated, convenient and safer route. Matrix tablets composed of drug and release retarding material offer the simplest approach in designing a sustained release system [31-35].

It is a weak acid (pKa = 4.7) practically insoluble in water and acidic environment but highly permeable (class 2) according to the biopharmaceutical classification system (BCS). The oral absorption is uniform, rapid and complete with a bioavailability of nearly 100% and an elimination half-life of 24 h[36-39].
Because of flexibility, hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Natural and semi-synthetic gums or polymers, such as guar gum, xanthan gum, hydroxypropyl methylcellulose, ethylcellulose, hydroxypropylcellulose, and sodium carboxymethylcellulose, are being used as release retarding materials27-28. Indeed, hydroxypropylmethylcellulose has received the most attention, likely due to its low toxicity and ease of manufacture [40].

Optimization

The word optimize is defined as to make as perfect, effective or functional as possible. During a development of a new project one generally experiments by a series of logical steps carefully controlling the variable & changing one at a time until a satisfactory result is produced. But under the circumstances the best one is often simply the last one prepared. It is satisfactory but how close is it to the optimum [41-45].

Used in optimization

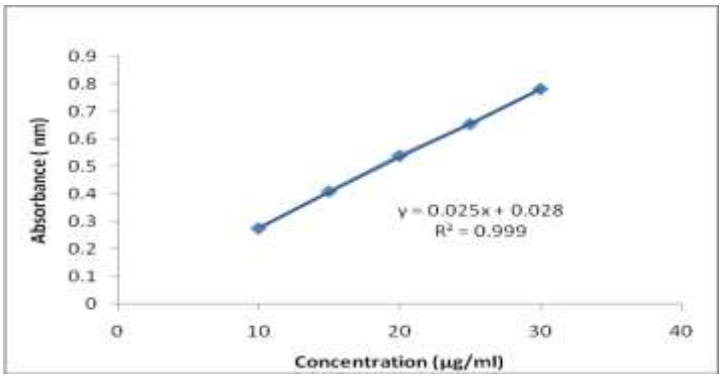
- **Variables** - These are the measurements, values, which are characteristics of the data. There are two types of variables, dependent and independent variables. Independent variables are the variables, which are not dependent on any other value e.g., concentration of lubricants, drug to polymer ratio, etc. Dependent variables are dependent on the concentration of independent variable used.
- **Factor -** Factor is an assigned variable such as concentration, temperature, lubricating agent, drug-to-polymer polymer-to-polymer ratio or grade. A factor can be qualitative or quantitative. A quantitative factor has a numerical value to it e.g., concentration (1%, 2% so on), drug to polymer ratio (1:1, 1:2 etc). Qualitative factors are the factors, which are not numerical, e.g., Polymer grades, humidity condition, type of equipment etc. These are discrete in nature.

- **Levels** - The levels of a factor are values or designation assigned to the factor, e.g., concentration 1% will be one level, while 2% will be another level. Usually levels are indicated as low, middle or high. Normally for ease of calculation the numeric and discrete levels are converted to -1 (low level) and +1 (high level).
- **Response -** Response is mostly interpreted as the outcome of an experiment. It is the effect, which are going to evaluate i.e., disintegration time, duration of buoyancy, thickness, etc.
- **Effect -** The effect of a factor is the change in response caused by varying the levels of the factor. This describes the relationship between factors and levels.
- **Interaction -** It is also similar to the term effect, which gives the overall effect of two or more variables (factors) of a response. For e.g. the combined effect of lubricant (factor) and glidant (factor) on hardness (response) of a tablet [46-50].

Preparation of Calibration Curve of Aceclofenac.

An UV spectrophotometer method was used for the estimation of aceclofenac in this work. A stock solution of aceclofenac (1000ug/ml) was prepared in 1.2 N Hcl and absorbance of aceclofenac was measured at 274.5 nm using schimanzo UV Vis spectrophotometer. As the dissolution studies were carried out in 0.1 N Hcl buffer, the standard concentration were prepared using the same medium of dilution in the range of 0-30 µg/ml of drug which obey the bee's Lambert law and calibration curve was constructed. The calibration data was given in the table below and curve was shown in the figure:

S.N.	Concentration (µg/ml)	Absorbance (274.5 nm)
1	0	0
2	10	0.275
3	15	0.409
4	20	0.539
5	25	0.654
6	30	0.781



Drug Excipients compatibility study (Physical observation)

The pure drug along with its formulation excipients were subjected to compatibility studies, result of the physical observation were shown in the following table.

Formulation Of Bi-Layered Tablet Of Aceclofenac:

The orally ingested bi-layered tablet of aceclofenac was prepared using Push Pull Technology. Two or three layer system a drug layer and push layer. Drug layer contain drug with other agents and due to this drug is less soluble. Sometimes suspending agent and osmotic agent are also added. The tablet core is surrounded by semi permeable membrane.

Evaluation Parameter of Bi-Layer Tablet of Aceclofenac Tablet

Solubility studies

Solubility studies were conducted in various solvent and different pH solutions. The solubility of API was determined by dissolving the drug in 250 ml of buffer. For the purpose purified water, organic solvent, 0.1 N Hcl solution, pH 6.8 phosphate buffer and pH 7.4 phosphate buffers were used. Specified amount of the pure drug was dissolved in 250 ml of medium and was kept for 12 hours. Insoluble drug was filtered off and the solution was analyzed in spectrophotometer to find out the solubility.

***In-vitro* dissolution studies**

The *in vitro* dissolution was carried out using USP Dissolution testing apparatus type-II (Paddle method; Veego Scientific VDA-8DR, Mumbai, India). The tablets were placed in the 0.1N hydrochloric acid for

first 1 hours and pH 6.8 phosphate buffers for next 6 hours respectively, and then the apparatus was run at 37°C±0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution medium. 10 ml of the sample was withdrawn at every hr interval for 6 h and the same volume was replaced with fresh dissolution media. The sample withdrawn was diluted to suitable volume with simulated gastric fluid and the absorbance was recorded at 273.5 nm using UV-VIS spectrophotometer.

Data analysis for release kinetics

To analyze the mechanism of drug release and release rate kinetics from the dosage form, the data obtained were fitted into zero order, first order, Higuchi release and Korsmeyer and Peppas release model.

Zero-Order release kinetics

To study the zero-order release kinetics the release rate data are fitted to the fallowing equation. F = K.t ----------1

Where, 'F' is the fraction of drug release, 'K' is the release rate constant and't' is the release time.

First – order release kinetics

To study the first-order release kinetics the release rate data are fitted to the fallowing equation. F = 100*(1 – e-Kt) ----------2

Where, 'F' is the fraction of drug release, 'K' is the release rate constant, 'e' is exponent coefficient and't' is the release time.

Table And Figures

Formulation details during primary development and optimization of immediate release layer using sodium starch glycolate:

Formulation	Weight per tablet (mg)						
Code	**Drug**	**SSG**	**PVPK30**	**Lactose**	**Mg –stearate**	**Talc**	**Colour**
AF1	5	13	20	30	1	1	0.01
AF2	5	18	20	25	1	1	0.01
AF3	5	21	20	22	1	1	0.01

SSG= Sodium starch glycolate, PVP= Polyvinylpyrrolidone,

Formulation details during primary development and optimization of sustained release layer using HPMC-K4M and PVP-K 30.

Formulation	Weight per tablet (mg)						
Code	**Drug**	**HPMC K4M**	**MCC**	**PVP-K 30**	**Lactose**	**Mg -Stearate**	**Talc**
AF1	30	36	-	20	40	2	2
AF2	30	33	8	20	35	2	2
AF3	30	30	10	20	36	2	2

HPMC=hydroxypropylmethylcellulose, MCC=microcrystalline cellulose

Formulation details during primary development of aceclofenac bi-layer tablets using sodium starch glycolate, HPMC-K4M and PVP-K 30.

	For immediate release layer				
S.N.	**Ingredient(mg/tab)**	**AF1**	**AF2**	**AF3**	**AF4**
1	Aceclofenac	5	5	5	5
2	Sodium starch glycolate	13	18	21	23
3	PVP-K 30	20	20	20	20
4	Lactose	29.99	24.99	21.99	19.99
5	Mg-stearate	1	1	1	1
6	Talc	1	1	1	1
7	Color	0.01	0.01	0.01	0.01
8	Total weight	70	70	70	70
	For sustain release layer				
9	Aceclofenac	30	30	30	30
10	HPMC K 4M	36	33	30	35
11	MCC	-	8	10	12
12	PVP-K30	20	20	20	20
13	LACTOSE	40	35	36	29
14	Mg-stearate	2	2	2	2
15	Talc	2	2	2	2
16	Total wt	130	130	130	130

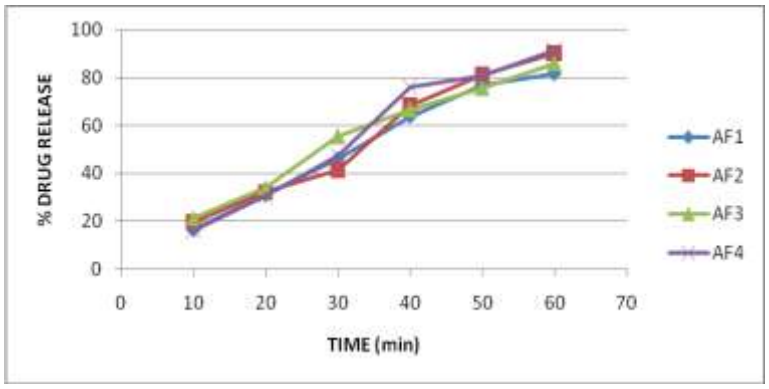
Post-compression parameter of bi-layer tablets:

Code	**Dimension**		**Hardness (kg/cm2)±S.D**	**Friability (%)±S.D**	**Weight Variation(gm) ±S.D**
	Diameter (mm)±S.D	**Thickness (mm)±S.D**			

AF1	9.48±0.035	3.43±0.023	6.34±0.061	0.22±0.017	199±1.44
AF2	9.52±0.024	3.45±0.033	7.92±0.045	0.14±0.018	198±1.36
AF3	9.53±0.022	3.47±0.026	7.61±0.034	0.21±0.021	201±1.48
AF4	9.51±0.015	3.46±0.021	7.11±0.032	0.24±0.012	200±1.46
AF5	9.49±0.038	3.44±0.031	7.10±0.047	0.33±0.015	200±1.45

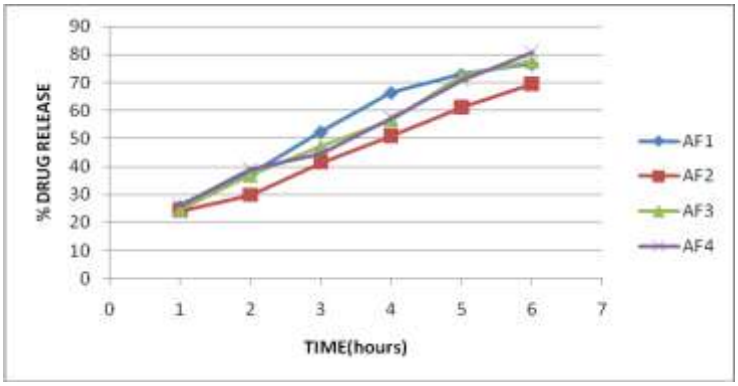
***In- vitro* release of Aceclofenac from immediate layer.**

Formulation Code	**Time in min (cumulative % drug release) 1.2 pH buffer**					
	10	20	30	40	50	60
AF1	16.68	31.21	46.21	64.03	77.15	81.84
AF2	19.5	32.15	41.5	68.25	81.37	90.2
AF3	21.37	34.03	55.59	66.84	75.75	86.06
AF4	16.21	30.75	47.62	76.21	80.9	91.68



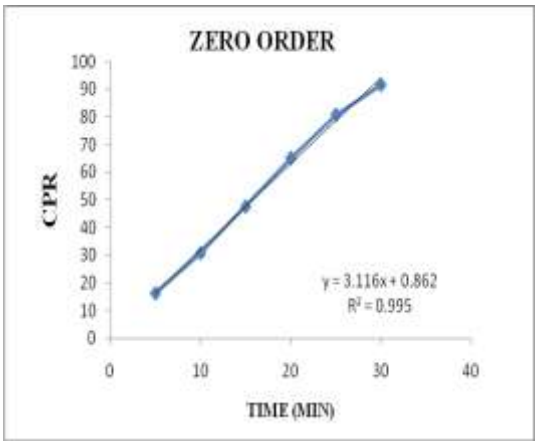
***In- vitro* release of Aceclofenac from sustain layer.**

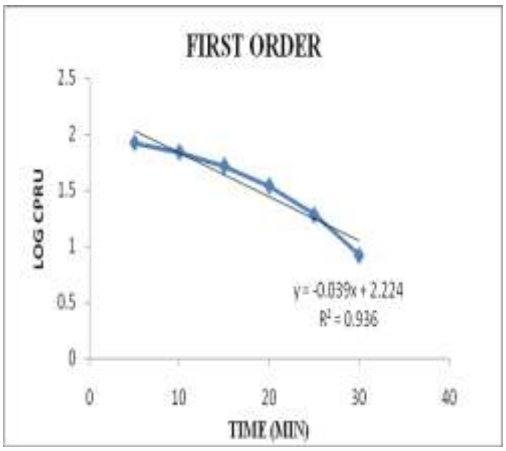
Code	**Time in min (cumulative % drug release) 6.8 pH buffer**					
	60	120	180	240	300	360
AF1	25.59	37.31	52.32	66.37	72.93	76.68
AF2	24.18	29.81	41.53	50.9	61.21	69.65
AF3	24.65	36.84	47.15	56.53	72.46	77.62
AF4	26.06	39.18	44.81	57.46	71.06	80.9

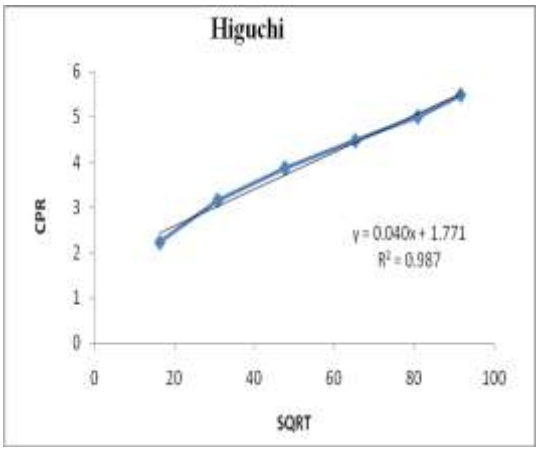


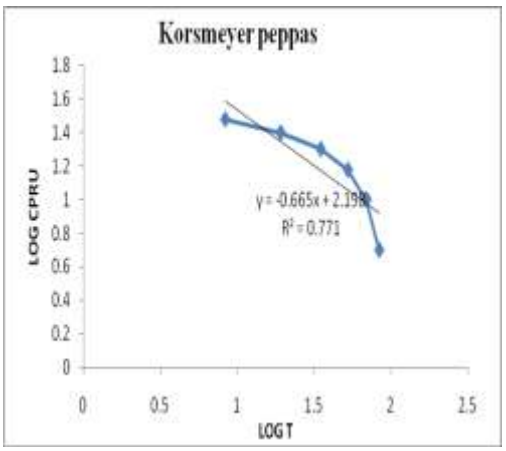
Release kinetics for immediate release formulation

Time	**Cum Release**	**CPRU**	**LOG CPRU**	**SQRT**	**LOG T**
5	16.21875	83.78125	1.923146836	2.236067977	0.698970004
10	30.75	69.25	1.840419778	3.16227766	1
15	47.625	52.375	1.719124036	3.872983346	1.176091259
20	65.2485	34.7515	1.540973555	4.472135955	1.301029996
25	80.90625	19.09375	1.280891232	5	1.397940009
30	91.6875	8.3125	0.919731658	5.477225575	1.477121255



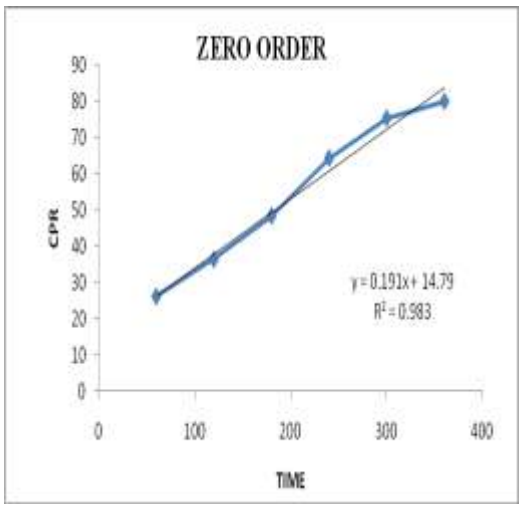


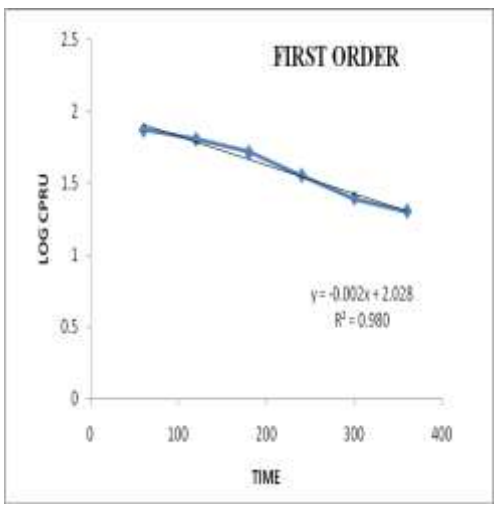


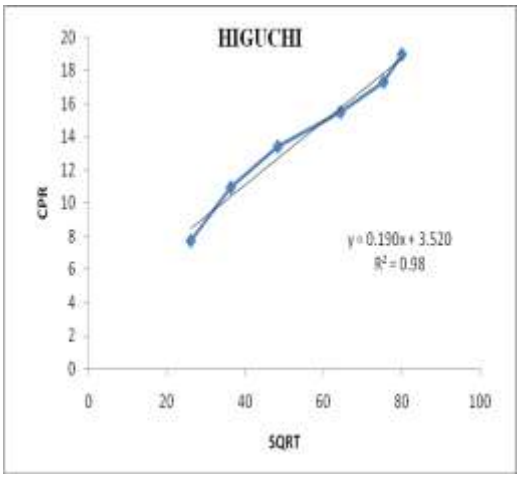


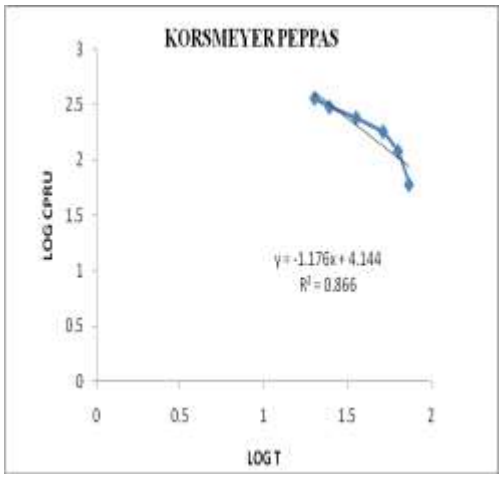
Release Kinetics For Sustain Release Formulation

TIME	CUM RELEASE	CPRU	LOG CPRU	SQRT	LOG T
60	26.06	73.94	1.868879446	7.745966692	1.77815125
120	36.27	63.73	1.804343918	10.95445115	2.079181246
180	48.256	51.744	1.713859998	13.41640786	2.255272505
240	64.25	35.75	1.553276046	15.49193338	2.380211242
300	75.25	24.75	1.393575203	17.32050808	2.477121255
360	79.863	20.137	1.30399477	18.97366596	2.556302501









III. Conclusion

In this work an attempt was made to formulate and evaluate bi-layer tablets of Aceclofenac as a model drug. The main objective of formulating bi- layer tablets was to achieve sustained release of Aceclofenac for long period of time so as to maintain the plasma drug concentration constant for the whole day. It also helps in decreasing the dosing frequency by which the patient compliance increases. For Aceclofenac it was known that it has a very short half life of only 4 h so in case of conventional tablets Aceclofenac dosing frequency was high. It also increases the patient incompliance. Drugs with short half life cannot maintain the plasma drug concentration at the therapeutic levels for a longer period of time. So as to decrease the dosing frequency and increase the patient compliance sustained release bi-layer tablets were designed.

The release of Aceclofenac from fast releasing layer was analyzed by plotting the cumulative percentage of drug release Vs time. It shows an effective initial burst effect from IR layer and released from this layer was completed within 30 mins. Formulations AF1, AF2, AF3 and AF4 were prepared by using SSG and PVP K30. In each formulation the quantity of SSG and PVP-K30 was varied to achieve the desired drug release profile and taken best four formulation of immediate release layer for selection best % drug release of Aceclofenac.In formulation AF1, which gave the drug release just 82% within 1 hours. In order to achieve greater drug release in formulation AF2, which gave the drug release just 90% within 1 hours.In formulation AF3, and AF4, the drug release from the formulation was found to 86%, and 91% within 1 hours. The formulation AF2 containing 18% of SSG and 20%w/w of PVP K30 was selected as the optimized batch since it showed the best drug release profile within 1 hours as compared to the other formulations. The release of Aceclofenac from second releasing layer was analyzed by plotting the cumulative percentage of drug release Vs time. Formulations AF1, AF2, AF3 and AF4 were prepared by using HPMC K 4M and PVPK30.

In each formulation the quantity of HPMC K 4M and PVP-K30 was varied to achieve the desired drug release profile and taken best four formulation of sustain release layer for selection best % drug release of Aceclofenac.In formulation AF1, which gave the drug release just 77% after 1 hours. In formulation AF2, AF3and AF4, the drug release from the formulation was found to 67%, 78%and 81% within 6 hours. The formulation AF4 containing 35% of HPMC K 4M and 20%w/w of PVPK30 was selected as the optimized batch since it showed the best drug release profile within 6 hours as compared to the other formulations.

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