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Research Article

Formulation and Evaluation of Ketorola Tromethamine and Rabeprazole Sodium Bilayere Matrix Tablets

KOTTA KRANTHI KUMAR*[1], GURU PRAKASH[1] , R.NAGAKISHORE[2]

[1]Department of Pharmaceutics, S.K.U College of Pharmaceutical sciences S.K.University, Anantapur.

[2] Geetangali college of pharmacy Hyderabad.

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ABSTRACT

Bilayer tablets were prepared by using combination of immediate release rabeprazole sodium along with sustained release ketorolac tromethamine. The FTIR study conducted using a combination of drugs along with excipients and polymers revealed that combination can be safely prepared. Rabeprazole sodium was formulated as immediate release layer using sodium starch glycolate, croscarmellose sodium, crospovidone as super disintegrants. The optimized rabeprazole sodium immediate release (IR 9) with highest in-vitro release was selected. Ketorolac tromethamine was formulated as sustained release layer using different grades of HPMC polymers and evaluated for in-vitro release studies. The optimized sustained release layer (F5) was selected. Bilayer tablets were prepared by double compression of optimized ketorolac tromethamine sustained release layer and rabeprazole sodium immediate release layer. All the physical parameters were in acceptable limit of pharmacopoeial specifications. Hence bilayer tablets of ketorolac tromethamine and rabeprazole sodium could be used to improve patient compliance towards the effective management of post operative pain, osteoarthritis without side effect of gastric irritation.

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INTRODUCTION

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explode for systemic delivery of drug via various pharmaceutical products of different dosage form. Popularity of oral route may be ease of administration as well as traditional belief that by oral administration the drug is well absorbed as food stuff ingested daily [1].

Multilayer tablets [2, 3]

This tablet consists of two or more layers of materials compressed successively in the same tablets. The color of each layer may be same or different. The tablets having layers of different colour are known as "multicolored tablets". Multilayer tablets are tablets mad by compressing several different granulations fed into a die in succession, one on the top of the, in layers. Each layer comes from a separate feed frame with individual weight control. Rotary tablet presses can be set up for two or three layers.

*Author for Correspondence:
Email: kranthijournal@gmail.com

Advantages of multilayer tablets

This dosage form has the advantage of separating two incompatible substances with an inert barrier between them.It makes possible sustained –release formulations with the immediate –release quantity in one layer and the slow release proportion in the second. A third layer, with an immediate release might be added. The weight of each layer can accurately controlled, in contrast to putting one drug of a combination product in a sugar coating. Two-layer tablets require fewer materials than compression coated tablets, weigh less, and may be thinner. Coloring the separate layer provides many possibilities for unique tablet identity.

Problems in layered tablets

Lack of proper bonding of two layers

Stress due to high compression force degrades certain actives e.g ramipril.

Bilayer tablets

Double layer (or bilayer) tablets have been around for recent time. Quite possibly the earliest uses of this dosage form were driven from a marketing perspective, with emphasis

placed on the perception of the consumer who would be utilizing the product. A tablet with two mutually exclusive "layers" represented by two clearly different colors ,provided manufacturers with a way to produce a product that looked more interesting than a standard white "pill".

Some novel bilayer and tri-layer tablet devices

a) Sustained release bilayer tablets

The multilayered tablet concept has been long utilized to develop sustained release formulations. Such a tablet ha s a fast releasing layer and may contain bi or tri layer to sustain the drug release. However blood level is maintained at steady state. Eudragit and ethyl cellulose have been used to obtain sustained release matrix formulations of different materials [4].

b) Bilayer and floating-bioadhesives tablets

A bilayer and floating bioadhesives drug delivery system exhibits a unique combination of floatation and bioadhesion to prolong residence time in the stomach. The sustained layer was compressed and granules of the floating layer were added to it, then both layers were compressed using a single station rotor press [5].

c) Tablet in capsule devices

It consists of an impermeable capsule body and a soluble cap. The multilayered formulations prepared is filled within the capsule body and sealed with the water soluble cap [6].

d) Three layered tablet system

To allow biphasic drug release, two layers contain a drug dose and an outer drug layer contains immediate available dose of drug. An intermediate layer made of swellable polymers, separates the drug layers. A film of impermeable polymer coats the layer containing the other dose of drug [7].

Bilayer problems [8]

- Layer separation
- Insufficient hardness
- Inaccurate individual layer weight control
- Cross contamination between the layers
- Reduced yield

Sustained Release Drug Delivery Systems [9-10]

Sustained release drug delivery systems can be defined as any dosage form that prolongs the therapeutic activity of the drug by continuously releasing medication over an extended period of time. In absence of suitable clinical evidence of this therapeutic effect it can be defined as any dosage forms that give prolongation of the drug levels in the blood. The major advantage of this category is that, in addition to the convenience of reduced frequency administration, it provides levels that are devoid of the peak and valley effect.

Extended Release Dosage Forms

A dosage form that allows at least a twofold reduction in dosage frequency as compared to that drug presented as an immediate-release (conventional) dosage form. Examples of extended-release dosage forms include controlled-release, sustained-release and long-acting drug products. Sustained release It includes any drug delivery system that achieves slow release of drugs over an extended period of time not particularly at a pre-determined rate.

Controlled release

It includes any drug delivery system from which the drug is delivered at a predetermined rate over a prolong period of time.

Delayed Release Dosage Form

A dosage form releases a discrete portion of drug at a time or times other than promptly after administration, although one portion may be released promptly after administration. Example: Enteric coated dosage forms.

Advantages of Sustained/Controlled Release Dosage Forms:

- Decreased local and systemic side effects reduced gastrointestinal irritation.
- Reduction in dosing frequency.
- Improved patient compliance and reduced patient care time.
- Reduced fluctuations in circulating drug levels

Disadvantages of Sustained/Controlled Release Dosage Forms:

- Unpredictable or poor in-vitro and in-vivo correlation.
- Dose dumping.
- Reduced potential for dosage adjustment.
- Poor systemic availability in general.

The aim of the present work is to formulate and evaluate bilayer tablets of rabeprazole and ketorolac tromethamine as bimodal release system to manage pain, osteoarthritis and to overcome the side effect of gastic irritation associated with NSAID treatment. Hence the present work proceeds with the following objectives.

Table 1: List of Materials[10,11]

Sl.No	MATERIAL	SOURCE
1	Ketorolac tromethamine	AP Scientific traders
2	Rabeprazole sodium	Bright scientific traders
3	Di calcium phosphate	A1 Standard Chemicals
4	Micro crystalline cellulose	AP Scientific traders
5	HPMC E15	AP Scientific traders
6	HPMC E50	AP Scientific traders
7	HPMC K15	AP Scientific traders
8	HPMC K100	AP Scientific traders
9	PVP K-30	Bright scientific traders
10	Guar gum	Bright scientific traders
11	Sodium starch glycollate	Bright scientific traders
12	Croscarmellose sodium	Bright scientific traders
13	Crospovidone	A1 Standard Chemicals
14	Magnesium stearate	A1 Standard Chemicals
15	Talc	A1 Standard Chemicals
16	Potassium dihydrogen phosphate	A1 Standard Chemicals
17	Hcl conc	A1 Standard Chemicals
18	Sodium hydroxide pellets	A1 Standard Chemicals

Table 2: List of Equipments

Sl.No	EQUIPMENT	SOURCE
1	Uv-Visible Spectrophotometer	Labindia Uv3000 Spectrophotometer
2	Digital Balance	Essae model fb 3000 digital balance.
3	Sensitive Balance	Keroy Km2 Sensitive Balance
4	P^H Meter	Labindia Ph Analyser
5	Tablet Punching Machine	Rimek Mini Press-II
6	Paddle Type Dissolution Apparatus USP	Labindia Ds 800
7	Fourier-Transformed Infrared (FTIR)Spectrophotometer	Perkin Elmer,Japan
8	Hardness Tester	Monsanto Ltd
9	Friability Apparatus	Labindia Ft 1020 Tablet Friability Tester
10	Disintegration Apparatus	Electrolab,mumbai.
11	Tray Dryer	Sisco Tray Dryer

- Preparation of immediate release layer of rabeprazole sodium using super disintegrants by direct compression methods.
- Preparation of sustained release layer of ketorolac tromethamine by using polymers like different grades of HPMC by direct compression methods, Physico-chemical characterization of drug and polymer by FTIR spectroscopy.
- Evaluation of parameters such as hardness, thickness, friability, weight variation, drug content uniformity for both immediate release and sustained release layer separately. Compression of immediate release layer and sustained release layer to make a bilayer tablet. *In-vitro* release study of both immediate release and sustained release layers separately.

MATERIAL AND METHODS[12-24]

Drug-polymer interaction study by FTIR spectroscopy

The drug-polymer and polymer-polymer interactions were studied by FTIR spectrometer. Perkin-elmer (spectrum-100) Japan. Two percent (w/w) of the sample, with respect to a potassium bromide disc, was mixed with dry KBr. The mixture was ground into a fine powder using an agate mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 psi. Each KBr disc was scanned 16 times at 2 mm/sec at a resolution of 4 cm-1 using cosine apodization. The characteristic peaks were recorded.

Preparation of sustained release layer of ketorolac tromethamine

Sustained release tablet layer was prepared by direct compression method according to the formula given in table. All the ingredients including drug were weighed accurately and passed through 60 mesh sieve separately. The drug and polymer was mixed by small portion of both each time and blend it to get a uniform mixture and kept aside. Then all the ingredients weighed and kept aside. Then all the ingredients weighed are mixed in geometrical order excluding magnesium stearate and talc to get a uniform blend. Finally mixture is blended with magnesium stearate and tablets were compressed of 9 mm sized concave round punch to get tablet using Rimek mini Press-I compression machine (Table 3).

Preparation of immediate release layer of Rabeprazole sodium

Rabeprazole sodium, dibasic calcium phosphate and poly vinyl pyrrolidone PVP K-30 (5%) were mixed with disintegrant for 15 min in porcelain mortar, passed through 60# sieve. This blend was mixed with magnesium stearate and talc for 5 min and processed for direct compression by using 9mm round concave-faced punch at 10 station tablet press. Compression force was maintained at constant level and magnesium stearate as lubricant was fixed at 1.16% w/w for all formulations. Disintegrants are used at 4, 6 and 8% in tablets. Compositions of all batches are represented in Table 4.

PREPARATION OF BILAYER TABLET [25-31]:

The bilayer tablets were prepared by double compression of optimized Ketorolac tromethamine sustained release layer (F5) and Rabeprazole sodium immediate release layer (IR9) using 9mm round punches on a Rimek tablet press.

EVALUATION OF BILAYERED TABLET [32-44]:

a) Weight variation
b) Thickness
c) Hardness
d) Friability
e) Drug Content uniformity
f) Disintegration time
g) *In vitro* Dissolution Studies

Weight Variation[44]

Twenty tablets were weighed collectively and individually. Average weight was calculated and based on the obtained weights % weight variation was calculated using the formula,

$$\% \text{ Weight Variation} = \frac{\text{Average weight} - \text{Individual weight}}{\text{Average weight}} \times 100$$

Hardness

Hardness of the tablet was tested by placing the tablet longitudinally in between the two plungers of the Monsanto tablet hardness tester and the obtained hardness was mentioned in terms of kg/sq.cm. Limits for Hardness are 4-6kg/sq.cm.

Friability

The friability of the tablets was determined by Roche Friabilator in which the tablets were subjected to the combined effect of abrasions and shock in a plastic chamber revolving at 25rpm and dropping the tablets at a height of 6 inches in each revolution. Pre weighed sample of tablets were placed in the friabilator and allowed to rotate for 100 revolutions. Later the tablets were deducted and the tablets were reweighed. Percent friability is given by the formula;

$$\text{Percent friability} = (1-W/W0) \times 100$$

Where W0 is the weight of the tablets before the test
W is the weight of the tablets after the test

Drug content uniformity for Rabeprazole sodium

The Rabeprazole immediate release tablets were assayed for the drug content using 0.1N HCl as the extracting solvent, and the samples were analyzed spectrophotometrically at 257nm. Six tablets were weighed and crushed in a mortar and their weighed powder containing equivalent to 50mg of drug transferred in 50ml of 0.1N hydrochloric acid. Its concentration is 1000 mcg/ml. 10ml from this stock solution was taken and diluted to 100ml with 0.1N HCl ,it makes 100µg/ml. Then 20µg/ml solution was prepared by taking 2ml from stock solution and diluted to 10 ml. The absorbance measured at 257 nm.

Table 3: Composition of Ketorolac tromethamine sustained release layer

Sl.No	Composition*	F1 Qty	F2 Qty	F3 Qty	F4 Qty	F5 Qty	F6 Qty	F7 Qty	F8 Qty	F9 Qty
1.	KETOROLAC	30	30	30	30	30	30	30	30	30
2.	HPMCE15	20	45	60	-	-	-	-	-	-
3.	HPMCK15									
4.	HPMCE50	-	-	-	20	45	60	-	-	-
5.	Guar gum	-	-	-	-	-	-s	20	45	60
6.	DCP	161.5	136.5	121.5	161.5	136.5	121.5	161.5	136.5	108.5
7.	MG stearate	5	5	5	5	5	5	5	5	5
8.	TALC	2	2	2	2	2	2	2	2	2
	TOTAL*	230	230	230	230	230	230	230	230	230

* All quantities in mg per tablet

Table 4: Composition of Rabeprazole sodium immediate releasing layer

Sl.No	Composition*	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
1.	KETOROLAC	20	20	20	20	20	20	20	20	20
2.	PVPK30	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5	8.5
3.	DCP	134.1	130.7	127.3	134.1	130.7	127.3	134.1	130.7	127.3
4.	CROS POVIDONE	3.4	6.8	10.2	-	-	-	-	-	-
5.	CSS	-	-	-	3.4	6.8	10.2	-	-	-
6.	SSG	-	-	-	-	-	-	3.4	6.8	10.2
7.	MGstearate	2	2	2	2	2	2	2	2	2
8.	TALC	2	2	2	2	2	2	2	2	2
	TOTAL*	170	170	170	170	170	170	170	170	170

* All quantities in mg per tablet

Drug content uniformity for Ketorolac tromethamine

The tablets were assayed for the drug content using methanol as the extracting solvent. Four tablets weighed and crushed in a mortar then weighed powder contain equivalent to 100mg of drug transferred in 100ml methanol. The solution was appropriately using ph 6.8 phosphate buffer and ketorolac tromethamine was estimated spectrophotometrically at 322nm using ph 6.8 phosphate buffers as blank.

Disintegration time

The disintegration test was performed using electro lab disintegrating apparatus. Placed one tablet in each of the six tubes of the basket and operate the apparatus using 0.1N HCl maintained at 37± 0.50c as the immersion fluid. Then note down the time to complete disintegration of tablets.

In vitro Dissolution Studies

Dissolution rate was studied by using USP type-II apparatus at 50 rpm using 900ml of 0.1N HCl solution as dissolution medium. Temperature of the dissolution medium was maintained at 37± 0.5^0C, aliquot of 5 ml of dissolution medium was withdrawn at every 10 min interval. The absorbance of solution was measured by uvspectroscopic method at 257 nm for

Rabeprazole sodium and at 322 nm for Ketorolac tromethamine. For ketorolac, for first 2hrs,0.1N HCl buffer solution was used as dissolution medium and then the dissolution medium was changed by replacing with ph 7.4 phosphate buffer solution for next 3 hours and then replacing 7.4 PH buffer with PH 6.8 phosphate buffer solution for further 7 hours. Concentration of drug was determined from standard calibration curve. The volume of the dissolution medium was adjusted to 900 ml at every sampling time by replacing 5 ml with same dissolution medium.

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

a) Zero order release model
b) First order release model
c) Hixson-crowell release model
d) Higuchi release model
e) Korsmeyer – peppas release model

a) Zero order release rate kinetics

To study the Zero order release kinetics the release rate data were fitted to the following equation.

$$F = K t$$

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

When the data is plotted as Cumulative percent drug released versus time, if the plot is linear then the data obeys Zero order release kinetics, with slope equal to K.

The results are given in table.

b) First order kinetics

A First order release would be predicated by the following equation.

$$\text{Log } C = \text{Log } Co - \frac{K t}{2.30\ 3}$$

Where = Amount of drug remained at time 't'
Co = initial amount of drug
K = First order rate constant (hr-1)

When the data is plotted as Cumulative percent drug remaining versus time yields a straight line, Indicating that the release follows First order kinetics .The constant 'K' can be obtained by multiplying 2.303 with slope value.

c) Higuchi release model

To study the Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = K. t1/2$$

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

When the data is plotted as Cumulative drug released Versus Square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K'.

d) Korsmeyer and peppas release model

The release rate data were fitted to the following equation.

$$Mt / M_{\infty} = K. t^{n}$$

Where, Mt / M_{∞} is the fraction of the drug release,
'K' is the release rate constant,
't' is the release time, and
'n' is the diffusional exponent for the drug release that is dependent on the shape of the matrix dosage form.

When the data is plotted as Log of drug released Versus log time, yields a straight line with a slope equal to 'n' and the, 'K' can be obtained from Y-intercept.

RESULTS

The overall observation of infrared study suggested that formulation development of drugs in combination with excipients, functionalities of drugs was un-reacted and hence contribution of drugs along with excipients can be formulated safely (Table 5 & 6; Fig. 1-5).

The disintegration time followed the order according to superdisintegrants as sodium starch glycolate < crospovidone < croscarmellose sodium. As the concentration of superdisintegrants was increased, there was a decrease in the disintegration time, which due to the fact that higher level of disintegrants probably made the large pores with continuous network of skeleton providing enough pressure within the matrix for faster disintegration. Hence the disintegration time for all the prepared layer was less than 1 min indicated that the prepared layer was immediate release in nature.

Table 5: Compatibility studies of Rabeprazole sodium with different excipients

Ingredients	Ratio	Initial Colour	After one week	After two weeks	After three weeks	After four weeks
			40 ^{0}C 75%RH	40 ^{0}C 75%RH	40 ^{0}C 75%RH	40 ^{0}C 75%RH
Rabeprazole sodium+PVP K30	1:1	Cream or white	Cream or White	Cream or White	Cream or White	Cream or white
Rabeprazole sodium +Dibasic calcium phosphate	1:1	White Powdered	White Powdered	White Powdered	White Powdered	White powdered
Rabeprazole sodium +Crospovidone	1:1	White Powdered	White Powdered	White Powdered	White Powdered	White Powdered
Rabeprazole sodium +Croscarmellose sodium	1:1	White Powdered	White Powdered	White Powdered	White Powdered	White Powdered
Rabeprazole sodium +Sodium starch glycolate	1:1	White Powder	White Powder	White Powder	White Powder	White powder
Rabeprazole sodium +Magnesium stearate	1:1	White Powder	White Powder	White Powder	White Powder	White Powder
Rabeprazole sodium +Talc	1:1	White Powder	White Powder	White Powder	White Powder	White powder

Table 6: Compatibility studies of Ketorolac tromethamine with different excipients

Ingredients	Ratio	Initial Colour	After one week	After two weeks	After three weeks	After four weeks
			40 ^{0}C 75%RH	40 ^{0}C 75%RH	40 ^{0}C 75%RH	40 ^{0}C 75%RH
Ketorolac tromethamine+HPMC E15	1:1	Cream or white	No change	No change	No change	No change
Ketorolac tromethamine +HPMC K 15	1:1	White powdered	No change	No change	No change	No change
Ketorolac tromethamine +HPMC E 50	1:1	White Powdered	No change	No change	No change	No change
Ketorolac tromethamine +Guar gum	1:1	White Powdered	No change	No change	No change	No change
Ketorolac tromethamine +Dicalcium phosphate	1:1	White Powder	No change	No change	No change	No change
Ketorolac tromethamine +Magnesium stearate	1:1	White Powder	No change	No change	No change	No change
Ketorolac tromethamine+Talc	1:1	White Powder	No change	No change	No change	No change

Table 7: Specifications of Weight Variation

Average weight as per USP	%Difference
130 mg or less	10
More than 130 mg through 324mg	7.5
More than 324mg	5

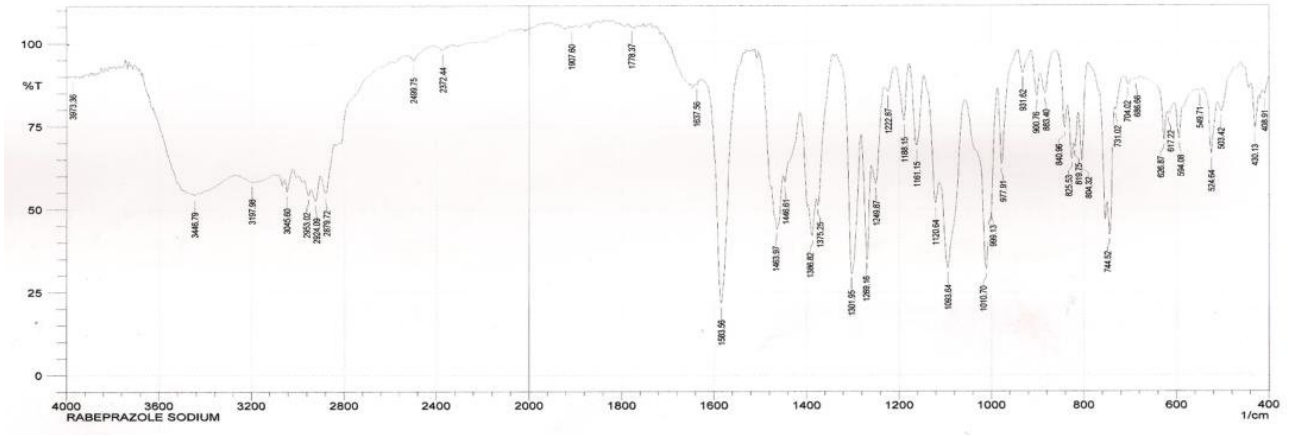

Figure 1: FTIR spectrum of rabeprazole sodium drug

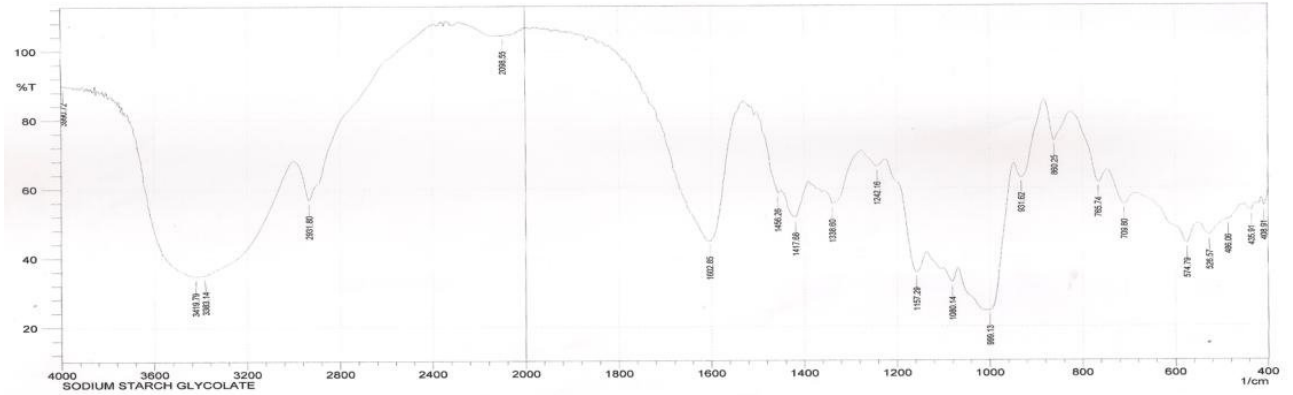

Figure 2: FTIR spectrum of sodium starch glycolate + Rabeprazole sodium

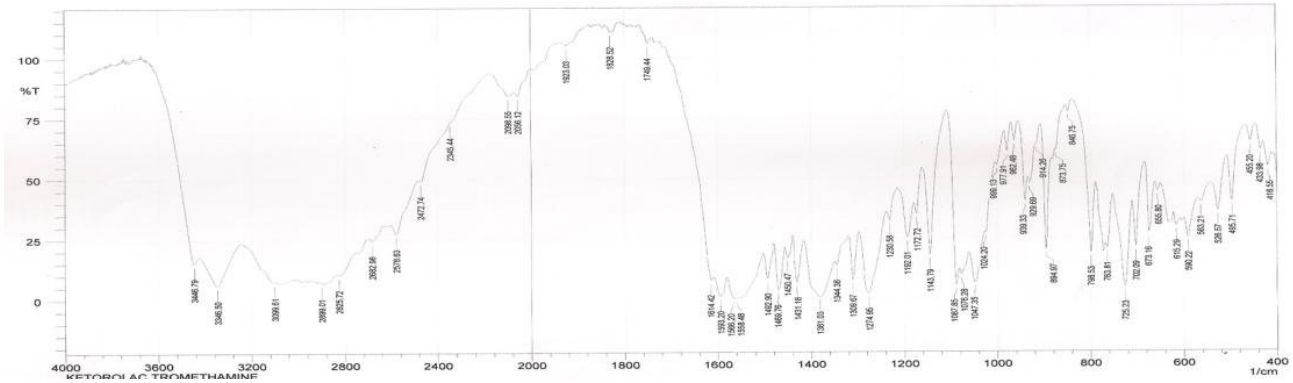

Figure 3: FTIR spectrum of ketorolac tromethamine drug

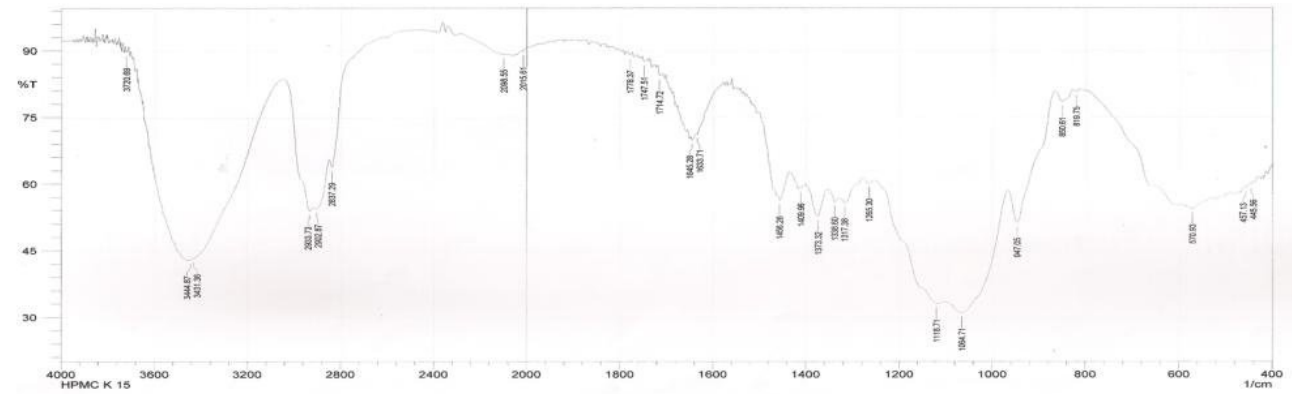

Figure 4: FTIR spectrum of HPMC K 15+ Ketorolac tromethamine

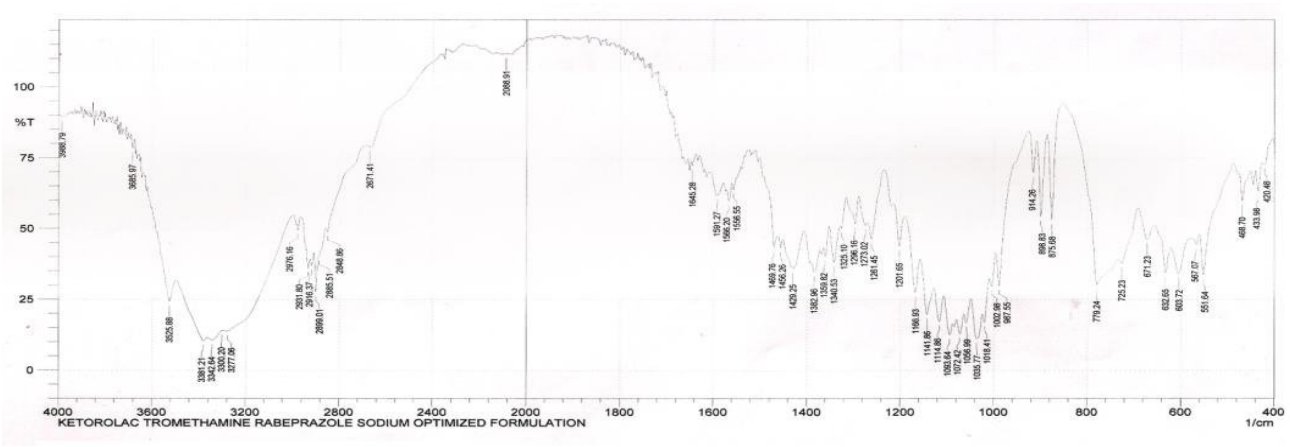

Figure 5: FTIR spectrum of optimized bilayer tablet formulation of Ketorolac tromethamine and Rabeprazole sodium

Table 8: Evaluation parameters of Rabeprazole sodium immediate release layer

Batch code	Hardness (Kg/cm²)	Thickness (mm)	% friability	Weight Variation	Drug content	*In-vitro* Disintegration time(sec)
IR1	3.46±0.05	2.24±0.05	0.43±0.05	170±0.02	99.10±0.90	38.66±1.15
IR2	3.40±0.00	2.30±0.00	0.33±0.05	170±0.05	98.99±0.90	35.33±1.15
IR3	3.43±0.05	2.23±0.04	0.40±0.01	171±0.01	99.19±0.54	31.66±1.00
IR4	3.50±0.00	2.24±0.05	0.56±0.05	170±0.02	99.81±0.36	46.66±1.52
IR5	3.56±0.05	2.24±0.05	0.56±0.05	170±0.02	99.81±0.36	46.66±1.52
IR6	3.53±0.11	2.19±0.03	0.50±0.05	170±0.01	100.71±0.57	40.66±1.15
IR7	3.76±0.05	2.27±0.04	0.16±0.05	170±0.57	98.85±0.80	31.00±2.88
IR8	3.70±0.00	2.24±0.05	0.20±0.00	170±0.54	99.10±0.90	27.66±2.42
IR9	3.83±0.05	2.23±0.04	0.20±0.00	170±0.02	100.29±0.90	22.66±2.51

Table 9: Evaluation parameters of Ketorolac tromethamine sustained release layer

Batch code	Hardness (Kg/cm²)	Thickness (mm)	% friability	Weight Variation	Drug content
F1	5.55±0.05	4.12±0.02 0	0.53±0.05	230±0.02	98.10±0.90
F2	5.96±0.01	4.21±0.01	0.50±0.00	230±0.05	98.21±0.90
F3	5.60±0.01	4.01±0.03	0.76±0.04	231±0.01	97.29±0.54
F4	5.00±0.05	3.86±0.02	0.43±0.05	230±0.02	98.01±1.27
F5	5.26±0.05	4.81±0.01	232±0.01	232±0.01	99.28±1.26
F6	5.36±0.05	4.71±0.02	0.63±0.03	230±0.51	97.23±1.80
F7	5.53±0.05	4.26±0.01	0.76±0.05	230±0.02	97.72±0.90
F8	5.63±0.05	4.33±0.02	0.23±0.02	231±0.02	99.29±0.90
F9	5.06±0.05	4.73±0.02	0.26±0.06	232±0.02	100.23±1.26

Table 10: *In-vitro* drug release profile of rabeprazole sodium layer

Time (min)	*In vitro* drug release								
	IR1	IR2	IR3	IR4	IR5	IR6	IR7	IR8	IR9
0	0	0	0	0	0	0	0	0	0
5	18.51	21.67	24.56	13.97	20.02	26.35	29.78	36.80	38.72
10	44.22	52.06	54.94	28.82	33.77	40.09	53.71	59.48	63.61
15	62.23	67.32	70.07	55.36	61.41	67.32	73.23	76.94	85.19
30	78.04	81.20	84.78	78.04	81.34	84.64	84.92	88.77	95.37
45	84.37	87.25	92.34	83.30	98.80	98.80	94.54	95.64	99.49
60	93.03	94.54	97.84	97.57	99.63	100.31	97.98	98.67	101.69
90	97.98	99.49	102.24	99.21	101.00	101.55	100.75	101.41	101.96

Table 11: *In-vitro* release data of Ketorolac tromethamine from different sustained release layers

Time (h)	In vitro drug release								
	F1	Fs2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
1	24.85	21.42	16.31	19.29	13.26	11.35	26.70	21.94	17.51
2	41.43	29.06	22.46	34.01	26.72	18.90	42.77	39.26	30.66
3	64.50	53.81	92.19	49.67	40.06	40.06	27.54	27.54	47.86
4	72.69	64.26	55.72	64.39	51.95	34.28	63.75	61.10	57.64
5	84.53	74.40	63.86	71.96	64.00	42.26	72.81	67.12	63.92
6	93.11	82.14	77.70	79.70	66.33	52.54	84.68	79.00	76.13
7	95.65	85.08	77.77	84.60	78.35	56.94	90.71	86.84	80.67
8	98.84	88.31	82.53	92.05	83.94	60.21	97.64	94.11	91.92
9	99.64	93.14	88.16	93.93	85.97	65.03	98.92	96.21	93.85
10	100.84	94.67	95.71	95.75	90.01	68.27	102.87	96.57	94.46
11	101.35	95.98	96.18	97.20	96.43	74.55	104.62	98.35	96.32
12	101.71	98.04	97.38	98.29	99.30	77.50	106.58	101.95	97.59S

The layer prepared by using crospovidone showed 97.98 to 102.24% drug release within 90 min. But after 15 mins, the release was ranged from 62.23 to 70.07%. The layer prepared by using croscarmellose sodium showed 99.21 to 101.55% drug release within 90 min. But after 15 mins, the release was ranged from 55.36 to 67.32%. The layer prepared by using sodium starch glycolate showed 100.73 to 101.96% drug release within 90 min. But after 15 mins, the release was ranged from 73.23 to 85.19%. Hence the layer containing SSG (6%) was confirmed as optimized layer which showed 85.19% release within 15 min. Hence based on the drug disintegration time and in vitro release study IR9 layer was selected as immediate release of rabeprazole sodium for further preparation of bilayer tablet.

The *in vitro* release study by Ketorolac tromethamine was conducted for 12 hrs, initially for 2hrs in 0.1N HCl, then for remaining 10 hrs in 6.8 PH phosphate buffer. The in-vitro release is depending upon the nature of drug, nature of polymer, drug to polymer ratio and the medium used. Experimental results showed that formulations F1, F2, F3 Containing drug: polymer (Drug:HPMC E15) in 3:2,2:3,1:2 showed drug release of 93.11%,82.14%,77.70% respectively at the end of 6th hr. Release profile of F1, F2, F3 were 101.71%,98.04%,97.38% respectively at the end of 12th hr. Formulations F4, F5, F6 Containing drug: polymer (Drug:HPMC K15) in 3:2,2:3,1:2 showed drug release of 79.50 %,68.94%,52.54% respectively at the end of 6th hr.

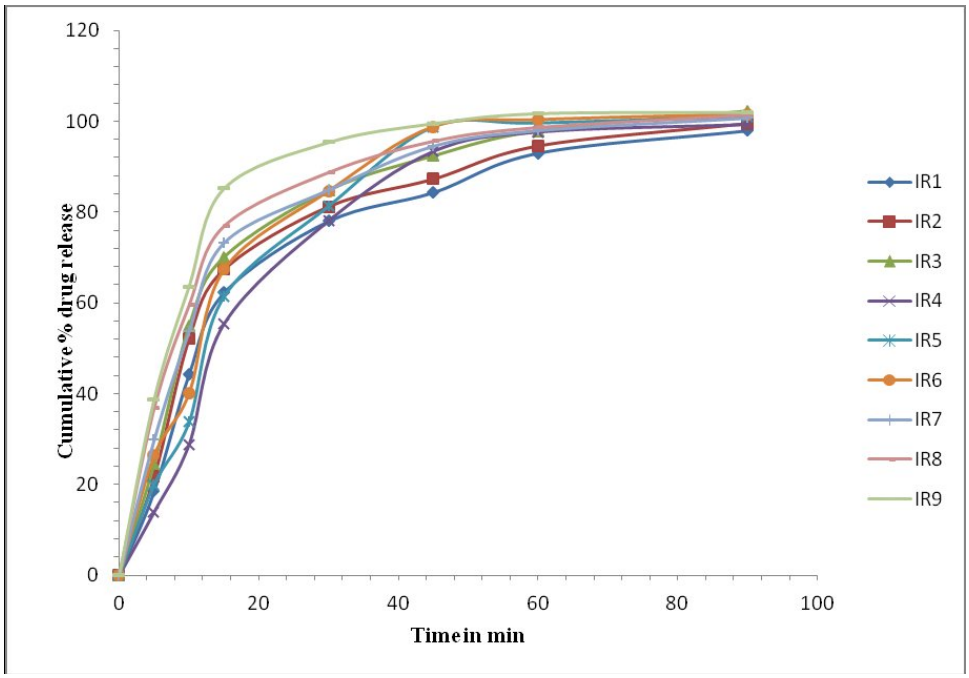

Figure 6: *In-vitro* release of Rabeprazole sodium from different immediate release layers

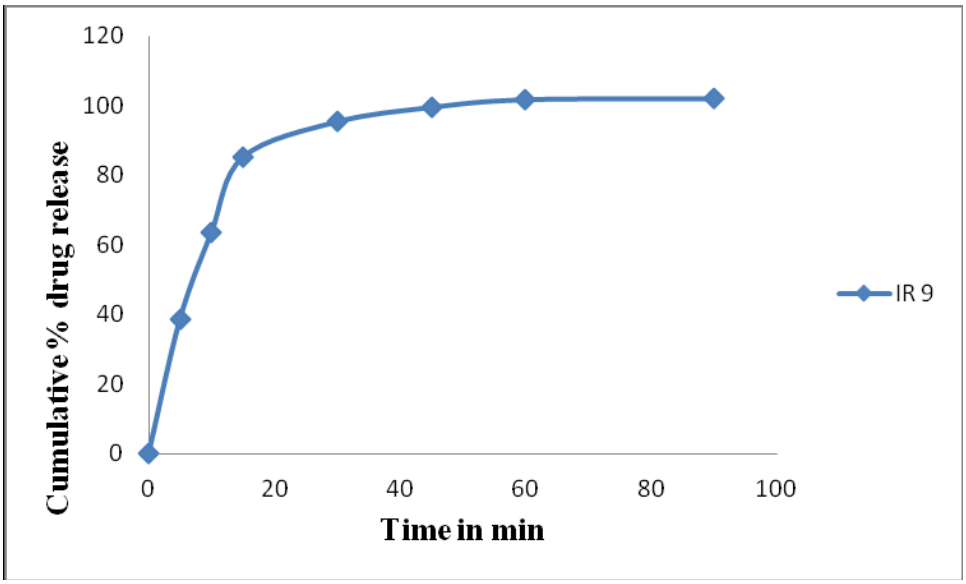

Figure 7: *In-vitro* release profile of optimized batch (IR9)

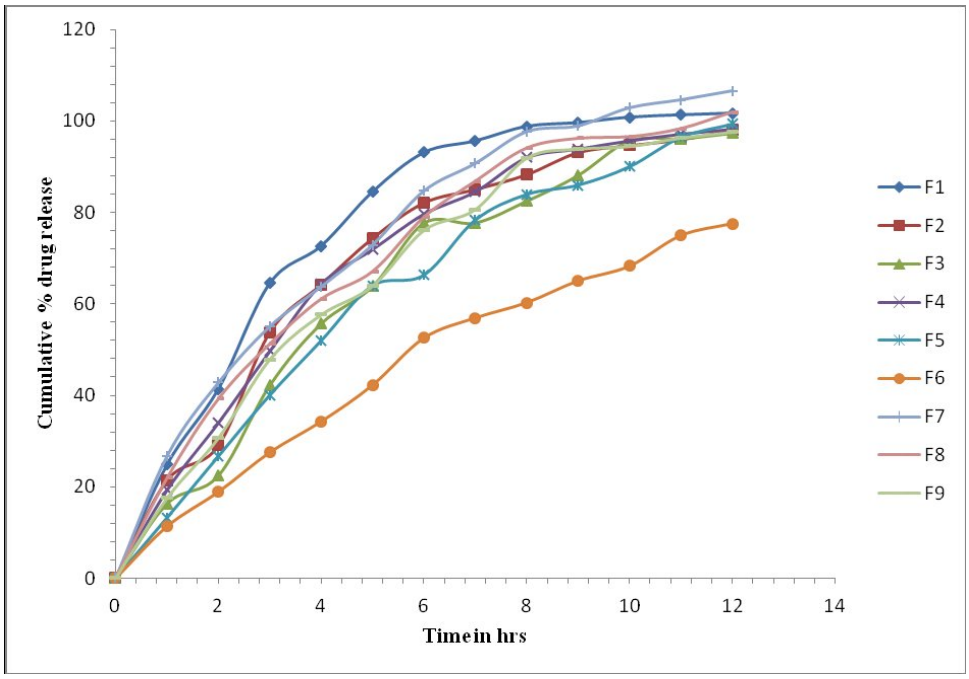

Figure 8: *In-vitro* release of ketorolac tromethamine from different sustained release layers

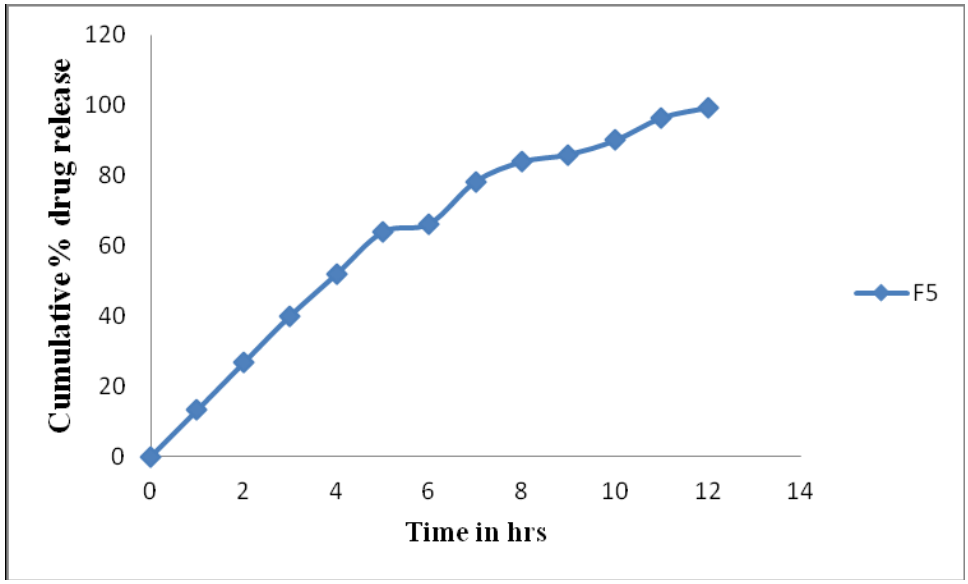

Figure 9: *In-vitro* release profile of optimized batch (F5)

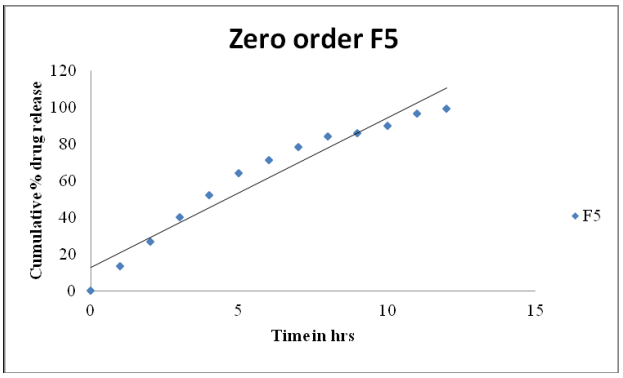

Figure 10: *In-vitro* release profile of optimized F5 according to Zero order kinetics

Figure 11: *In-vitro* release profile of optimized F5 according to First order kinetics

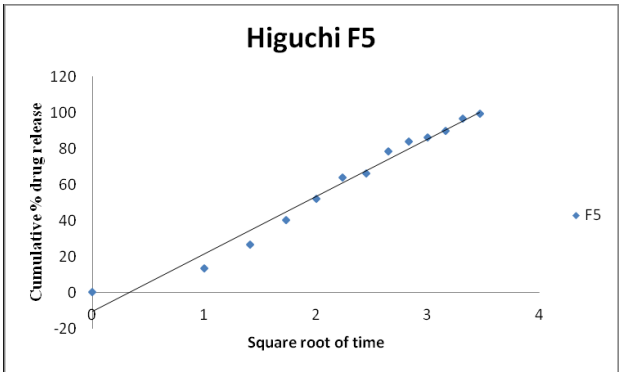

Figure 12: *In-vitro* release profile of optimized F5 according to Higuchi model

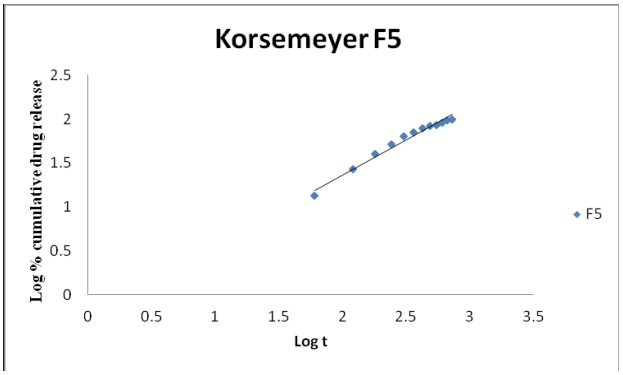

Figure 13: *In-vitro* release profile of optimized F5 according to Korsemeyer model

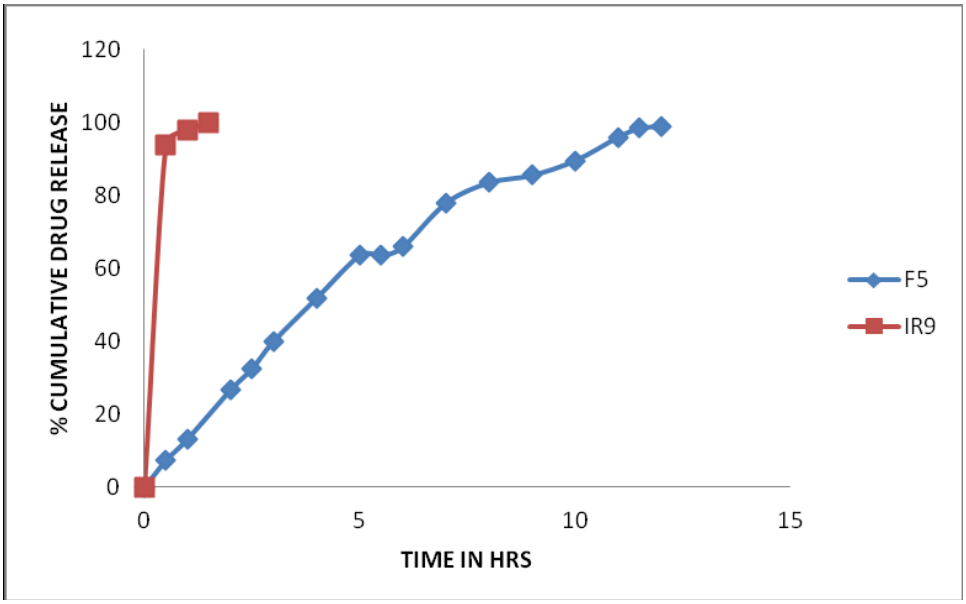

Figure 14: *In-vitro* drug release pattern of optimized bilayer tablet of Ketorolac tromethamine and Rabeprazole sodium

Table 12: Regression analysis and 'r2' values of the in vitro release data according to various release kinetic models

BATCH CODE	ZERO	HIGUCHI	PEPPAS	FIRST	PEPPAS n VALUE
F1	0.9557	0.9654	0.9556	0.9688	0.6084
F2	0.9781	0.9497	0.9127	0.9848	0.6624
F3	0.9908	0.9193	0.8715	0.9684	0.7688
F4	0.9802	0.9603	0.903	0.9876	0.6249
F5	0.9980	0.9324	0.9096	0.3857	0.8220
F6	0.9963	0.9401	0.9007	0.992	0.8113
F7	0.9598	0.9902	0.955	0.9924	0.5777
F8	0.9582	0.9832	0.9735	0.9978	0.6449
F9	0.9770	0.9607	0.9539	0.9948	0.7462

Release profile of F4, F5, F6 were 98.29%,99.80%,77.56% respectively at the end of 12th hr. Formulations F7, F8, F9 Containing drug: polymer (Drug:HPMC E50) in 3:2,2:3,1:2 showed drug release of 84.68 %,79.00%,76.13% respectively at the end of 6th hr.Release profile of F7, F8, F9 were 106.58,101.95,97.59 respectively at the end of 12th hr. Best release was observed for prolonged period of time with HPMC K15 as the polymer in 2:3 ratio with drug in F5 formulation.

The *in vitro* release data from sustained release layer was subjected to zero order (percent drug release vs. time), first order (logarithm of percent drug remaining vs time), higuchi (fraction of drug release vs. square root of time), korsmeyer peppas (log percent drug release vs log time). The goodness of best fit was evaluated by regression analysis of the above said models. The correlation coefficient 'r2' according to all the models is mentioned in table 20. The kinetics of in vitro release from all formulated sustained release layer obeyed zero order with high regression 'r2' value of 0.998 to 0.9557 as compared to first order which showed less ' r2' values. As polymers used were matrix in nature, hence Higuchis model was applied which showed good linearity with high regression 0.9193 to 0.9902 suggested that the release mechanism was diffusion controlled. The in-vitro release data was subjected to korsmeyer peppas model which shows good linearity with high 'r2' value of 0.8715 to 0.9735 and 'n' value is in the range of 0.5777 to 0.822 which indicated non Fickian (anomalous) transport refers to a combination of both diffusion and erosion controlled-drug release. Hence from the overall study of Ketorolac tromethamine sustained release layer F5 was selected for preparation of bilayer tablet.

SUMMARY AND CONCLUSION

The bilayer tablet was prepared by double compression. Rabeprazole sodium was formulated as immediate release layer using crospovidone, croscarmellose sodium and sodium starchglycolate as super disintegrants in different concentrations and Ketorolac Tromethamine was prepared as sustained release layer using matrix forming polymers like different grades of HPMC. The in-vitro release profile of bilayer tablet containing immediate release layer of rabeprazole sodium and sustained release layer of Ketorolac Tromethamine was estimated using simultaneous estimation method and it showed optimum release of both drugs for desired time periods respectively.

CONCLUSION

Hence bilayer tablets of rabeprazole sodium and Ketorolac Tromethamine as immediate and sustained release combination would be used to improve patient compliance towards the effective management of pain,osteo arthritis and post operative pain without the side effect of gastric irritation.

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