JOURNAL OF PHARMACEUTICAL SCIENCE AND BIOSCIENTIFIC RESEARCH (JPSBR)

(An International Peer Reviewed Pharmaceutical Journal that Encourages Innovation and Creativities)

Formulation, Optimization and Evaluation of Bilayer Matrix Tablet of Lornoxicam and Thiocolchicoside

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ABSTRACT:

The objective of present work is to formulate, optimize and evaluated of bilayer tablet of Lornoxicam and Thiocolchicoside. In this study Lornoxicam is in immediate release layer and Thiocolchicoside is in sustain release layer. For immediate release layer sodium starch glycolate was used as supredisintigration. And Sustain release layer Xanthan gum was used. The bilayer matrix tablet is evaluated by measuring Hardness, Thickness, Diameter, in vitro drug release study, Weight variation, % drug content. FT-IR studies were also indicating the absence of strong interactions between the components and suggesting drug-excipient compatibility in all the formulations examined. 32 full factorial designs were used in present study for optimization. Amount of Xanthan gum and amount of PVPK-30 M was used as an independent variable and % drug release was used as dependent variable. From the result formulation L4 was optimize which given the % drug release at 30 min 99.02 %. For sustain release layer check point batch was optimize which gives % drug release at 8 hr 93.19 %.

KEY WORDS: Lornoxicam, Thiocolchicoside, Bilayer matrix, Rheumatoid arthritis.

Article history:

Received 26 Aug 2015
Revised 09 Sept 2015
Accepted 14 Sept 2015
Available online 15 Oct 2015

Citation:

Patel A., Varu M., Prajapati P., Jadhav A. B. Formulation, Optimization and Evaluation of Bilayer Matrix Tablet of Lornoxicam and Thiocolchicoside. **J Pharm Sci Bioscientific Res**. 2015 5(5): *494-503*

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INTRODUCTION:

Bilayer tablet is new concept for successful development of sustained release formulation along with various features to provide a way of successful drug delivery system that include an immediate release (IR) layer and an Sustained release (SR) layer.[1] Immediate release layer provide therapeutically effective plasma drug concentration for a short period of time and Sustained release (SR) layer maintain uniform drug levels over a sustained period to reduce dosing intervals and side effects, increase the safety margin for highly-potent drugs and thus offer better patient compliance.[2]Advantages of bi-layer tablets Greatest chemical and microbial stability compared to other oral dosage forms. Bi-layer tablet is suitable for preventing direct contact of two drugs and thus to maximize the efficacy of combination of two drugs. Bi-layer tablets can be designed in such a manner as to modified release as either of the layers can be kept as extended and the other as immediate release. Patient compliance is improved leading to improve drug regimen efficiency. Disadvantages of Bi-Layer Tablet Dosage form. Difficult to swallow in case of children and unconscious patients. Some drugs resist compression into dense compacts, owing to amorphous nature, low density character. Drugs with poor wetting, slow dissolution properties, optimum absorption high in GIT may be difficult to formulate or manufacture as a tablet that will still provide adequate or full drug bioavailability. Bitter testing drugs, drugs with an objectionable odor or drugs that are sensitive to

oxygen may require encapsulation or coating. [3,4]

Rheumatoid arthritis is an autoimmune disease in which there is joint inflammation, synovial proliferation and destruction of articular cartilage. Immune complexes composed of IgM activate complement and release cytokines (mainly TNF α and IL -1) which are chematactic for neutrophils.[5,6] RA is a chronic progressive ,crippling disorder with a waxing and waning course. NSAIDs are the first line drugs and affort symptomatic relief in pain ,swelling , morning stiffness ,immobility , but do not arrest the disease process.The goals of drug therapy in RA are:a)Ameliorate pain, swelling and joint stiffness.b)Prevent articular cartilage damage and bony erosions.c)Prevent deformity and preserve joint function. [7-10]

Inhibition of the enzyme cyclo-oxygenase (COX).COX converts the fatty acid, Arachidonic acid in to endoperoxides, prostaglandins and Thromboxanes in a cell specific manner. NSAIDs act by direct inhibition of COX -1 and COX -2, via blockade of the COX enzyme site. Thus subsequent inhibition of PGs reduces inflammation. So reduce the pain by inhibiting the release pain inducing prostaglandin.

MATERIALS AND METHODS:

MATERIALS:

Lornoxicam is obtained from Alkem Industry Mumbai. Thiocolchicoside Macloeds Pharma Ltd. All other excipient used to prepare tablets was of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

METHODS:

Direct compression:

Drug(Lornoxicam), polymer were passed through a 20# sieve. After all ingredients were weight accurately. All ingredients except the lubricant were mixed thoroughly. Lubricant added and mix up to 15 min.

Wet granulation method:

Drug(Thiocolchicoside), polymer and other ingredients were weighed accurately. All ingredients except the binder and lubricant were mixed thoroughly. PVP K30 M was dissolved in sufficient quantity of isopropyl alcohol and added to a powder mixture to prepare dough wet mass. The prepared wet mass was passed through a 10# sieve. The granules were allowed to dry in a hot air oven and then resifted through a 20# sieve. The granules were collected and other ingredients were added and lubricated. Tablets were compressed by a 8.25 mm diameter flat punch with the help of a rotary tablet compression machine. From the preliminary study xanthan gum is selected as sustain release polymer. [11-14]

Table 1: Preliminary screening for optimization of immediate release layer:

Ingredients	**Formulation(mg)**					
	L1	L2	L3	L4	L5	L6
Lornoxicam	8	8	8	8	8	8
Sodium starch glycolate	2	3	4	5	6	7
Sodium bicarbonate	30	30	30	30	30	30
Microcrystalline cellulose	25	25	25	25	25	25
Lactose monohydrate	84	83	82	81	80	79
Aerosil	1	1	1	1	1	1
Total	150	150	150	150	150	150

Experimental design: 3^2 factorial designs: [15-18]

Table 2: Variables for factorial design

Independent variable	**Dependant variable**	
X1	X2	
Xanthan gum	PVPK-30 M	% Drug release after 4 hr % Drug release after 8 hr

Table 3: Coding values of full factorial batches

Coding value	**-1**	**0**	**+1**
Amount of Xanthan gum	40 mg	45mg	50mg
% of PVP K-30 M	3%	4%	5%

Evaluation of factorial batches:

Angle of Repose

Angle of repose has been defined as the maximum angle possible between the surface of Pile of powder and

Table 4: Optimization of batch using 3^2 full factorial designs:

Ingridient	Formulation(mg)								
	T1	T2	T3	T4	T5	T6	T7	T8	T9
Thiocolchicoside	8	8	8	8	8	8	8	8	8
Xanthan gum	40	40	40	45	45	45	50	50	50
PVP K-30 M	4.5	6	7.5	4.5	6	7.5	4.5	6	7.5
Lactose momohydrate	96.5	95	93.5	91.5	90	88.5	86.5	85	83.5
Aerosil	1	1	1	1	1	1	1	1	1
Total	150	150	150	150	150	150	150	150	150

horizontal plane. The angle of repose for the granules of each Formulation was determined by the funnel method. The prepared granules were allowed to flow out of the funnel orifice fixed at a height of 2 cm from the surface on a plane Paper kept on the horizontal platform. The gradual addition of the granules from the funnel mouth forms a pile of granules at the surface this is continued until the pile touches the stem tip of the funnel. A rough circle is drawn around the pile base and the radius of the granule cone was measured. Angle of repose was then calculated with the use of the following formula:

$$\tan \theta = h/r$$

Where, θ= angle of repose

h= height of the pile

r = average radius of the powder cone

Table 5: Relationship between Angle of repose (θ) and flow ability

Angle of repose (θ)	Flow ability
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very poor
>66	Very very poor

Bulk Density

Bulk density of the granules was determined by pouring gently 10g of sample through a glass funnel into a 50ml graduated cylinder. The volume occupied by the sample was recorded. The bulk density will be calculated as follows:

Bulk Density (gm/ml) = Weight of sample in grams/ volume occupied by the sample

Tapped Density

10 grams of granule sample was be poured gently through a glass funnel into a 50ml Graduated cylinder. The cylinder will be tapped from height of 2 inches until a constant volume will be obtained. Volume occupied by the sample after tapping will be recorded and tapped density will be calculated as follows:

Tapped Density (g/ml) =Weight of sample in grams/Volume occupied by the sample

Carr's Index

One of the important measures that can be obtained from bulk and tapped density determinations is the percent compressibility or the Carr's index, I, which is determined by the following equation,

C.I. =Tapped density − Bulk density/Tapped density × 100

Table 6: % Compressibility and its significance:

% Compressibility	Flowability
5-15	Excellent
12-16	Good
18-21	Fairly acceptable
23-35	Poor
33-38	Very poor
>40	Not acceptable

Hausner's ratio

Hausner's ratio is defined as a ratio of a tapped density to bulk density. It is a measure of relative importance of interparticulate interactions. A Hausner ratio greater than 1.25 is considered to be an indication of poor flowability.

Tapped density and bulk density were measured and the Hausner's ratio was calculated using the formula,

Hausner s ratio =Tapped density/Bulk density [19, 20]

Table 7: Specification for Hausners ratio

Hausner's ratio	Flowability
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very very poor

Characterization of bilayer Matrix tablet:

Weight Variation

The weight of the tablet is routinely measured to ensure that the tablet contains proper Amount of drug. 20 tablets were taken at random for the test and were weighed, individually and the average weight was calculated. The % deviation of each tablet from the average weight was calculated.

Table 8: Specifications for weight variation test

Sr. No	Avg. wt. of tablet	% of deviation allowed
1	80 mg or < 80	10%
2	> 80 but < 250 mg	7.5%
3	250 mg or more	5%

Hardness

Tablets require a certain amount of strength, or hardness, to withstand the mechanical shocks of handling in manufacturing, packaging as well as in shipping. The hardness of the tablets here was measured using a simple Monsanto hardness tester. In this, a tablet is placed between the plungers, and was tightened from one end, and pressure required to break the tablet diametrically was measured.

Friability

In this test 10 tablets was weighed and placed in a Roche Friabilator test apparatus, and then the tablets was subjected to rolling and repeated shocks, resulting from free falls within the apparatus from the height of 6 inches. After 100 revolutions the tablets will be removed, de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

% friability = 1 – (wt. of tablets after test/ wt. of tablets before test) x 100

Dimensions

A compressed tablet's shape and dimensions will be determined by the tooling during the compression process.

Thickness

Thickness is the only dimensional variable related to the process. The dimension of tablets was measured using the Vernier caliper scale. Tablet thickness should be controlled within a ±5% variation of the mean value. [21, 22]

Disintegration test

Disintegration test is a method to evaluate the rate of disintegration of tablets. It is also defined as break down of solid dosage form into smaller particles when it is disintegrated. Place 1 tablet in each of the 6 tubes and added a disc to each tube. Maintain the temperature of the disintegration media at 37±2ºC as specified in the monographs. At the end of time limit specified, left the basket from fluid and observe the tablets. If 1 or 2 tablets fail to disintegrate completely repeat the test on 12 additional tablets. Not less than 16 out of 18 tablets tested disintegrate completely.

Ten tablets were finely powdered and an amount equivalent to 100 mg of Lornoxicam was accurately weighed and transferred to a 100 ml volumetric flask, then 70 ml of buffer pH 1.2 (0.01N HCL) was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper (No.41) and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for Lornoxicam content at 262 nm using a double beam UV/Visible spectrophotometer and 0.1N HCL as blank.

Ten tablets were finely powdered and an amount equivalent to 100 mg of Thiocolchicoside was accurately weighed and transferred to a 100 ml volumetric flask, then 70 ml of phosphate buffer pH 6.8 was added. The flask was shaken for 10 minutes. Finally, the volume was made up to the mark with the same buffer solution. The resultant solution was then filtered through Whatman filter paper (No.41) and 1 ml of the filtrate was suitably diluted up to 100 ml with same buffer solution and analyzed for Thiocolchicoside content at 289 nm using a double beam UV/Visible spectrophotometer and phosphate buffer 6.8 as blank.

In-Vitro dissolution studies:

The in vitro dissolution was carried out using USP Dissolution testing apparatus type-II (Paddle). The tablets were placed in the 0.1N hydrochloric acid for first 2 hours and pH 6.8 phosphate buffers for next 8 hours respectively, then the apparatus was run at 37°C±0.5°C and a rotating speed of 50 rpm in a 900 ml dissolution

medium. The 5 ml aliquots were withdrawn at intervals of 5 minutes, 10 minutes, 15 minutes, 20, minutes, 25 minutes, 30 minutes, 1 hour, 2 hours,3 hours,4 hours, 5 hours, 6 hours, 7 hours, 8 hours, and replacement was done each time with equal amounts of fresh dissolution medium maintained at same temperature. Each 5 ml aliquot was filtered through Whatmann filter paper. 1 ml of sample was diluted to 5 ml 0.1N HCL for first 2 hours and then with pH 6.8 phosphate buffers for next 8 hours and absorbance was measured at 262 nm for Lornoxicam and after 2 hr taken for Thiocolchicoside at 289 nm using UV spectrophotometer . Drug concentrations in the sample were determined from standard calibration curve.

RESULT AND DISCUSSION:

Compatibility study of Lornoxicam with Thiocolchicoside: All the characteristic peaks of drug were observed in FTIR spectra of physical mixers of both drug are shown in Fig1. FTIR study showed that the drugs were not interacting with each other.

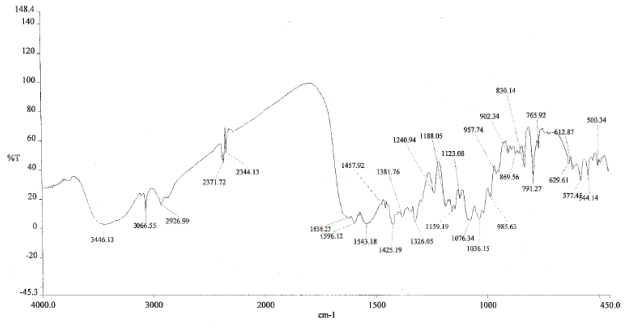


Fig 1: FTIR spectrum of combination of drugs Lornoxicam and Thiocolchicoside.

Evaluation parameters of preliminary screening:

Table 9 : Pre compression parameters for immediate release layer

Batch No. Ratio	Bulk Density(gm/ml) (Mean ± SD)	Tapped Density(gm/ml) (Mean±SD)	Angle of Repose (Mean ±SD)	Carr's Index (%)	Hausner ratio
L1	0.2246±0.006	0.2466±0.0057	21.10±0.57	8.921	1.097
L2	0.2236±0.006	0.2466±0.0057	22.333 ±0.57	9.32	1.102
L3	0.2263±0.006	0.2366±0.0057	23.666 ±0.57	4.35	1.04
L4	0.2253±0.006	0.2533±0.0057	22.333 ±0.58	11.05	1.124
L5	0.2243±0.006	0.2566±0.0057	23.666 ±0.58	12.58	1.144
L6	0.2253±0.007	0.2433±0.0057	22.333 ±0.57	7.39	1.079

Table 10 : Pre compression parameters of sustain release layer.

Batch No. Ratio	Bulk Density(gm/ml) (Mean ± SD)	Tapped Density(gm/ml) (Mean±SD)	Angle of Repose (Mean± SD)	Carr's Index (%)	Hausner ratio
T1	0.2812±0.002	0.3214±0.0057	17.66±0.5773	12.50	1.14
T2	0.2578±0.004	0.3104±0.0067	17.33±0.5773	16.94	1.20
T3	0.2963±0.005	0.3457±0.0057	18.33±0.5773	14.28	1.16
T4	0.3015±0.004	0.3676±0.0057	18.33±1.527	17.98	1.21
T5	0.2739±0.003	0.3125±0.0057	18.33±0.5773	12.35	1.14
T6	0.2951±0.001	0.3521±0.0057	19.00±1.000	16.18	1.19
T7	0.2642±0.006	0.3109±0.0057	18.33±0.5773	15.02	1.17
T8	0.2578±0.004	0.2987±0.0067	17.66±0.5773	13.69	1.15
T9	0.2987±0.007	0.3642±0.0057	18.33±0.5773	17.98	1.21

Evaluation of Post- compression parameters of bilayer tablet :

Evaluation of tablet properties:

Table 11 - Evaluation of tablet properties for bilayer tablet.

No of trial	Avg.Tablet Wt (mg) (n=3)	Thickness (mm) (n=3)	Hardness Kg/cm^2 (n=3)	Friability (%)
B1	298.5	4	4.33	0.8%
B2	301.3	4	4.66	0.7%
B3	300.8	4	4.33	0.8%

B4	299.4	4	5	0.6%
B5	297.3	4	4.33	0.7%
B6	300.9	4	5	0.8%
B7	302.6	4	5	0.9%
B8	301.7	4	4.66	0.7%
B9	299.2	4	5	0.9%

Assay for Lornoxicam and Thiocolchicoside:

TABLE 12 : Assay of Lornoxicam and Thiocolchicoside

No. of trial	Assay(%) Lornoxicam	Assay(%)Thiocolchicoside
B1	98.21	98.21
B2	97.89	99.78
B3	98.74	98.34
B4	99.01	99.01
B5	98.23	98.21
B6	99.23	97.89
B7	97.78	97.88
B8	98.90	98.23
B9	98.34	99.21

In vitro Dissolution Profile

Table 13 : Evaluation Parameters of Preliminary screening of immediate release:

Formulation	Disintegration test (min)	% Cumulative Drug release at 30 min
L1	15	85.22± 3.43
L2	11	89.66±2.12
L3	9	92.24±2.07
L4	3	99.02±2.27
L5	3.4	98.55±2.74
L6	3.2	99.43±1.19

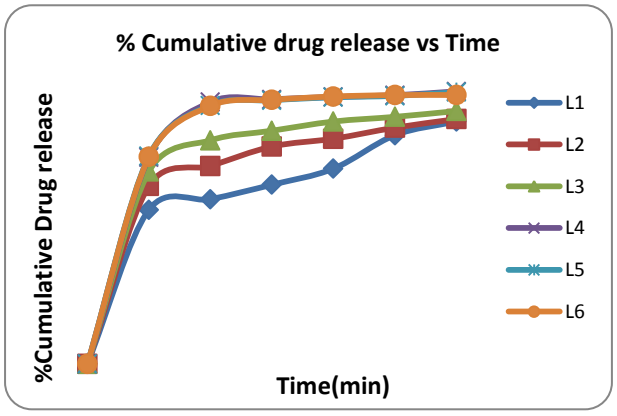


Fig 2: In vitro dissolution profile of formulation of L1 –L6

Table 14: - Dissolution profiles of trial T1-T9

Batch	% Cumulative Drug Released at 8 hr (n=3)
T1	97.67± 1.56
T2	98.19±1.79
T3	98.00±2.18
T4	98.63±1.75
T5	95.40±4.34
T6	87.21±3.5
T7	90.35±4.30
T8	87.33±4.93
T9	85.33±4.12

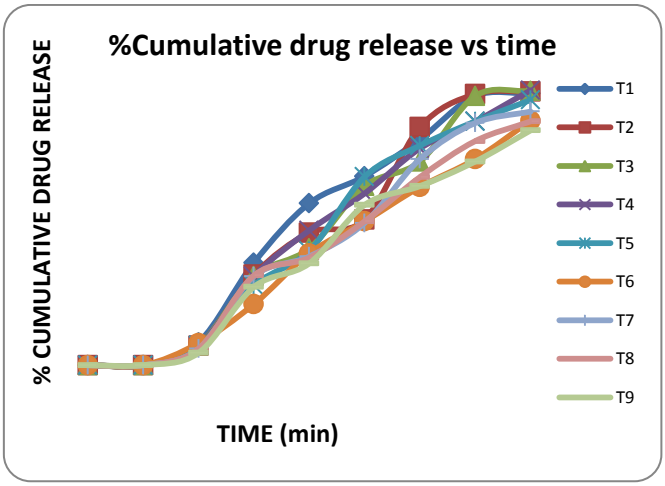


Fig 3: In vitro dissolution profile of formulation of T1 –T9

Analysis of Experimental Design:

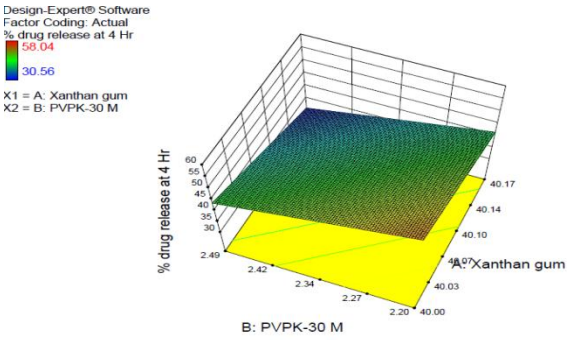
Response: 1 (% drug release at 4 hr):

Best fitted model

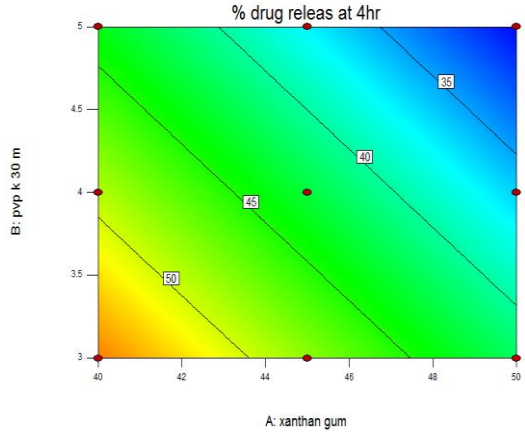
Table 15: Summary of Experimental design response 1

Equation	Sequential p value	Adjusted R squared	Predicted R squared	
Linear	0.0007	0.8832	0.7757	Suggested
Quadratic	0.9224	0.8577	0.4165	
Cubic	0.5135	0.8875	-1.5636	
2F1	0.1562	0.9099	0.7691	

3 D Plot of Raft strength Vs Independent variables



Counter plot of % Drug release Vs Independent variables:



Coded equation

$42.77 - 6.54 * X_1 - 5.48 * X_2$

Final equation in term of Actual Factor

123.5011 - 1.30733*Xanthangum - 5.47500*PVP K-30 M

Conclusion

From actual factor equation and Counter plot of % Drug release at 4 hr Vs independent variable it was concluded that as amount of Xanthan gum and PVP K-30 M increases, % Drug release is decrease.

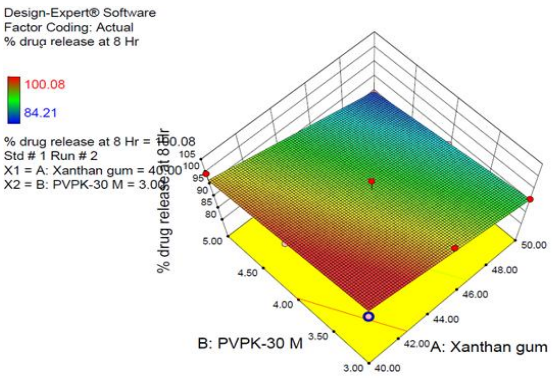
Response 2 (% Drug release at 8 hr)

Best fitted model

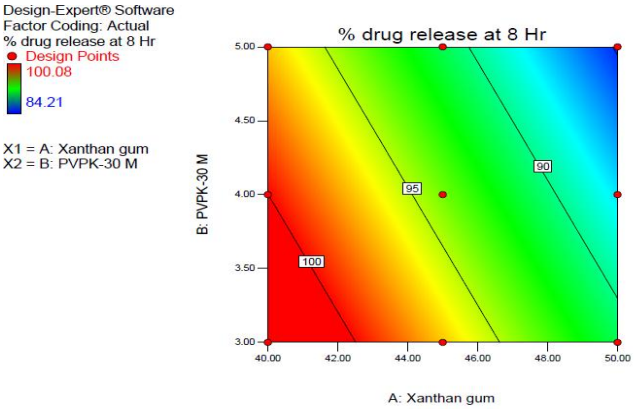
Table 16: Summary of Response 2

Equation	Sequential p value	Adjusted R squared	Predicted R squared	
Linear	0.0021	0.8280	0.7131	Suggested
Quadratic	0.7638	0.7794	0.1256	
Cubic	0.5842	0.7741	-4.1462	
2F1	0.2734	0.8416	0.6685	

3 D plot of % drug release Vs independent variables:



Counter plot of % drug release Vs Independent variables:



Coded equation

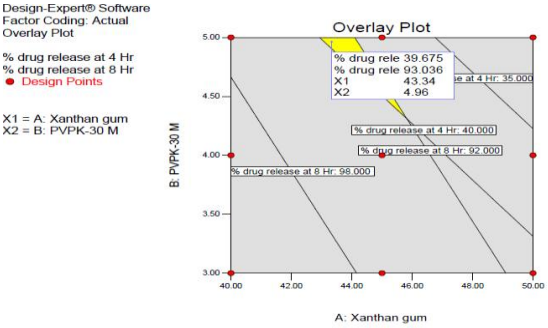
$93.94 - 6.07 * X_1 - 3.04 * X_2$

Final equation in term of Actual Factor

160.75333 – 1.21467 *Xanthan gum – 3.033833 * PVP K 30 M

From actual factor equation and Counter plot of % Drug release at 8 hr Vs independent variable it was concluded that as amount of Xanthan gum and PVP K-30 M increases, % Drug release is decrease.

Overlay Plot



OPTIMIZED FORMULATION

Table 17: Formulation of optimize bilayer matrix tablet

Ingridient	Quantity taken (mg)
For Immediate release layer	
Lornoxicam	8
Sodium starch glycolate	5
Sodium bicarbonate	30
Microcrystalline cellulose	25
Lactose monohydrate	81
Aerosil	1
For Sustain release layer	
Thiocolchicoside	8
Xanthan gum	43.34
PVP K-30 M	4.96
Lactose momohydrate	92.7
Aerosil	1
Total	300

Evalution for bilayer tablet of optimized batch:

In vitro Dissolution profile of optimize batch:
Medium: 0.1N HCL(2 Hr), phosphate buffer 6.8 pH(up to 8 hr)
Apparatus : Paddle (usp type- II)
RPM : 100
Volume : 900ml

Table 18: For immediate release layer

Sr.no	Time (min)	%cumulative drug release(n=3)
1	0	0
2	5	75.84 ± 2.51
3	10	94.17±1.27
4	15	96.31±2.29
5	20	97.52±2.10
6	25	98.27±1.66
7	30	99.50±1.69

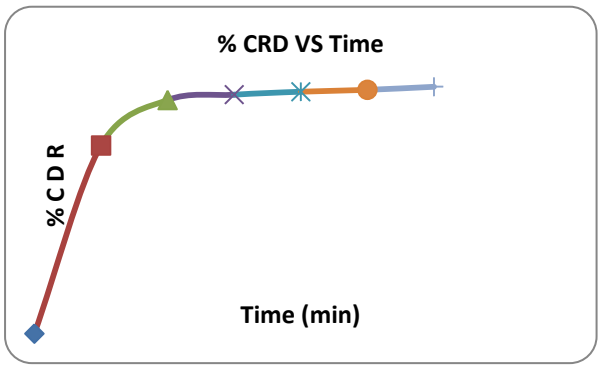


Fig 4 : In vitro dissolution profile of optimize batch

Table 19:In vitro drug release profile of sustain release layer

Sr.no	Time (hr)	% cumulative drug release
1	0	0
2	1	0
3	2	9.14 ± 3.28
4	3	35.09 ± 3.08
5	4	43.36 ±4.18
6	5	51.03 ±2.15
7	6	73.49 ± 2.09
8	7	88 .00 ± 2.64
9	8	93.19 ± 2.51

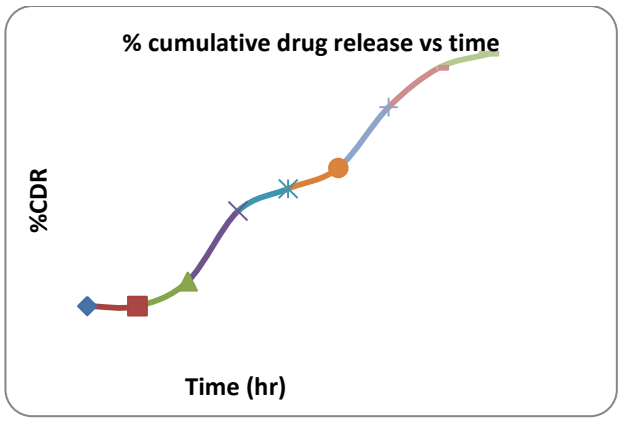


Fig 5 : In vitro dissolution profile of formulation of T1 –T9

CONCLUSION:

A conclusion can be drawn that bilayer matrix forming tablet was prepped by using matrix forming agent Xanthan gum and for immediate layer sodium starch glycolate. The evaluation parameter like weight variation, Thickness, Hardness, friability , % drug release ,drug content were showing satisfactory results. Optimize was carried out using experimental design and the batch showed parameter in range with specification. Thus, it can be said that matrix forming tablet of Lornoxicam and Thiocolchicoside can be used in treatment of Rheumatoid arthritis which is a common problem faced by most patients.

ACKNOWLEDGEMENT:

The author would like to give a privilege to the Managing trust of SMT BNB Swaminarayan Pharmacy College, Salvav and the Principal Dr Anil Jadhav for providing excellent facilities and deep support for carrying out the research work. The Author would also present a token of thanks to Guide Mrs. Anuradha Patel and HOD, Pharmaceutics Mr. Ajay Talele as this work would not

have been possible without his keen interest and support. The author would also thankful to parents and dear friends.

Conflict of Interest:
The author shows no conflict of interest.

Abbreviations and Symbols:
RA – Rheumatoid arthritis
NSAIDs- Non steroidal anti inflammatory drugs
PGs :Prostaglandin
PVP- Polyvinyl pyrollidone
SR- sustain release
IR-Immediate release
TNF- Tissue narcotic factor
IL- Interleukin
mg- miligram
gm- Gram
C.I- Carr's index
nm-nanometer

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