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Formulation and Evaluation of Sustained Release Tablet of Etodolac

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Original Research Article

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Abstract: Sustained release formulations are becoming more popular now days for the delivery of non-steroidal anti-inflammatory drugs (NSAIDs) because of their ability to maintain therapeutic effective drug concentration for prolonged duration with low dosing frequency and side effects associated with NSAIDs. The present study was attempted to develop Sustained release tablets of a model NSAID drug, Etodolac. Etodolac Sustained release tablets were prepared by Gellan Gum (A, mg), Sodium CMC (B, mg), Xyloglucan (C, ml), Xanthan Gum (D, ml), MCC (E, ml), Talc (F, rpm), Orange flavour (G, rpm), Aspartame (H, rpm), Magnesium stearate (I, rpm). The granules were evaluated for flow properties by evaluating bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. The tablets were evaluated for drug polymer compatibility study by FTIR, diameter, weight variation test, hardness, friability, disintegration test, SEM, Swelling Index, In vitro drug release, release kinetics, stability studies and Plackett-Burman Experimental Design was also applied to find the optimized formulation. The FTIR study revealed that no such interactions being taking place in between drug and polymers. The flow property of granules of all tablet batches was found to be good. All the tablet formulations had good tablet physiochemical properties. The swelling of the tablets was also found optimum. From the results of in-vitro study, it was concluded that Etodolac Sustained release tablet provided most sustained release of Etodolac over extended period of time with aid of greater stability.
Keywords: Sustained, Plackett-Burman, NSAIDs, therapeutic effect, Etodolac.

INTRODUCTION

Usually conventional dosage forms produce wide ranging fluctuation in drug concentration in the blood stream and tissues with consequent undesirable toxicity and poor efficiency. These factors as well as factors such as repetitive dosing and unpredictable absorption led to the concept of controlled drug delivery systems. The goal in designing sustained or controlled delivery systems is to reduce the frequency of dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So controlled release dosage form is a dosage form that releases one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Controlled release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery.

Physico-chemical characterization

Physico-chemical parameters of the obtained sample of drug were analyzed and reported

Calibration curve

Calibration curve was constructed for Etodolac in distilled water at 279 nm using UV-visible spectrophotometer and the absorbance values with mean and standard deviation were reported.

Fourier Transform Infrared (FTIR) Spectral analysis:

FTIR spectra of pure drug and physical mixture of drug and excipients were recorded on samples prepared in potassium bromide (KBr) disks using a FTIR Spectrophotometer, (FTIR-8300, and Shimadzu, Japan). Samples were prepared in KBr disks by means of a hydrostatic press at 6-8 tons pressure. The scanning range was 400 to 4000 cm^{-1}.

Differential Scanning Calorimetry (DSC) analysis

DSC analysis was performed using Shimadzu DSC-60, Shimadzu Limited Japan. A 1:1 ratio of drug and excipient was weighed into aluminium crucible. And sample was analysed by heating at a scanning rate of 20°C over a temperature range 40-430°C under nitrogen environment

Formulation and design of experimental batches

The PBD factorial design of experiment was performed using Design-Expert® software (Version-6.0.8, Stat-Ease Inc., and Minneapolis, MN). PBD plotted twelve runs containing variation value of factors. The significance of the design was determined

by the comparison of statistical parameters, and on the basis of higher values of R^2. Two-dimensional (2D) contour plots and three-dimensional (3D) response plot resulting from the equations having higher factor values were constructed using Design- Expert® software.

Different ingredients of formulation and processing factors were Gellan Gum (A, mg), Sodium CMC (B, mg), Xyloglucan (C, ml), Xanthan Gum (D, ml), MCC (E, ml), Talc (F, rpm), Orange flavour (G, rpm), Aspartame (H, rpm), Magnesium stearate (I, rpm), and dummy factors.

Factor	Name	Unit	Low Actual	High Actual
A	Gellan Gum	mg	50	150
B	Sodium CMC	mg	50	150
C	Xyloglucan	ml	50	150
D	Xanthan Gum	ml	50	150
E	MCC	ml	111	211
F	Talc	mg	03	05
G	Magnesium stearate	-	8	10
H	Aspartame	-	10	12
I	Orange flavor	-	10	12
J	(dummy factor)	-	-1	1
K	(dummy factor)	-	-1	1

Sustained release matrix tablets of etodolac were prepared by using natural gums xanthan gum, gellan gum, sodium CMC and tamarind xyloglucan at different PBD batch (F1 to F12) ratios.

The Plackett-Burman Experimental Design matrix (in coded level) and experimental runs

Batches	A	B	C	D	E	F	G	H	I	J	K
F1	150	150	50	50	111	5	8	12	12	-1	1
F2	50	150	50	150	211	3	10	12	12	-1	-1
F3	50	50	50	150	111	5	10	10	12	1	1
F4	50	150	150	150	111	3	8	12	10	1	1
F5	**150**	**50**	**150**	**150**	**111**	**5**	**10**	**12**	**10**	**-1**	**-1**
F6	150	50	150	150	211	3	8	10	12	-1	1
F7	150	150	50	150	211	5	8	10	10	1	-1
F8	50	50	50	50	111	3	8	10	10	-1	-1
F9	50	150	150	50	211	5	10	10	10	-1	1
F10	50	50	150	50	211	5	8	12	12	1	-1
F11	150	50	50	50	211	3	10	12	10	1	1
F12	150	150	150	50	111	3	10	10	12	1	-1

Tablets were prepared by wet granulation method using formulas of different experimental batches [1-5].

Swelling index

The extent of swelling was measured in terms of % weight gain by the tablet. The swelling behaviour of all formulation was studied. One tablet from each formulation was kept in a Petri dish containing pH 6.8 phosphate buffers. At the end of 2, 4, 6, 8, 10 and 12 hrs tablets were withdrawn, soaked on tissue paper and weighed and then percentage weight gain by the tablet was calculated and swelling index was determined [6-8].

In vitro drug release studies

Drug release study was carried out by using USP dissolution rate test apparatus-II (Electrolab, Mumbai, India). The study was conducted at 37°C and 50 rpm in 900 ml pH 6.8-phosphate buffer and studied for drug release up to 12 h. Five ml of sample was withdrawn at different time intervals, filtered and the drug content was estimated at 226 nm after suitable dilution [9-11].

Scanning Electron Microscopy

The optimized formulation (F10) was selected for Scanning Electron Microscopy (SEM) analysis. The tablet surface morphology was studied at zero time and 12^{th} hour of dissolution. The morphological characters of these 2 scans were compared to hypothesize the mechanism of drug release and swelling [12-15].

Stability Studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. In the

present study, stability studies were carried out at 40°C±2°C/75%±5% RH for a period of 90 days for the selected formulations. The formulations were then evaluated for changes in the physicochemical properties, swelling study and *in vitro* drug release [16-19].

RESULT & DISCUSSION

Physico-chemical characterization Calibration curve

Calibration curve has showed linearity with a correlation coefficient (R^2) of 0.9994 as shown in Figure 6.

Table-1: Physico-Chemical parameter observation of Etodolac

Sr. No.	Parameter	Observation
1	Color	White
2	Taste	Bitter
3	State	Amorphous
4	Solubility	Freely soluble in water, sparingly soluble in alcohol and isopropyl alcohol
5	Melting point	145-148 ^{0}C

Table-2: Calibration table of Etodolac in distilled water at 279 nm

S. No.	Concentration (µg/ml)	Absorbance+ SD
1	0	0
2	2	0.13±0.1
3	4	0.25±0.1
4	6	0.38±0.1
5	8	0.49±0.1
6	10	0.62±0.1

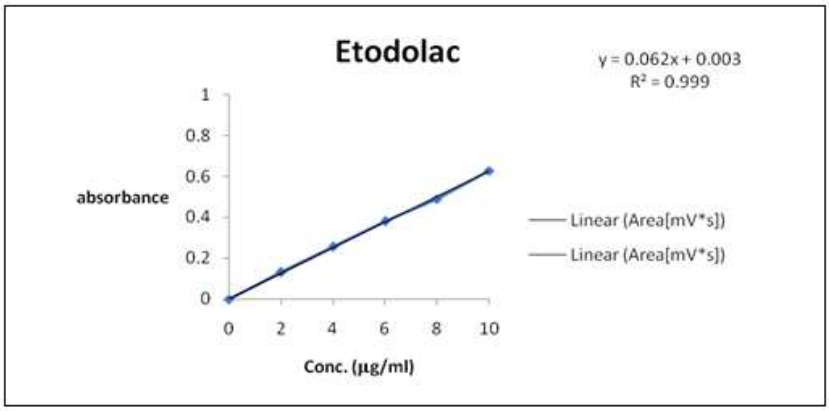


Fig-3: Calibration curve of Etodolac.

Fourier Transform Infrared (FTIR) Spectral analysis

Physical mixture of ketorolac and formulate ingredients were subjected for IR spectroscopic analysis to ascertain whether there was any interaction between drug and excipients used. The IR spectra showed similar characteristic peaks at their respective wavelengths with minor differences. The similarity in the peaks indicated the compatibility of drug with formulation excipients. IR spectra of the physical mixture of drug with formulate ingredients were depicted in figure.

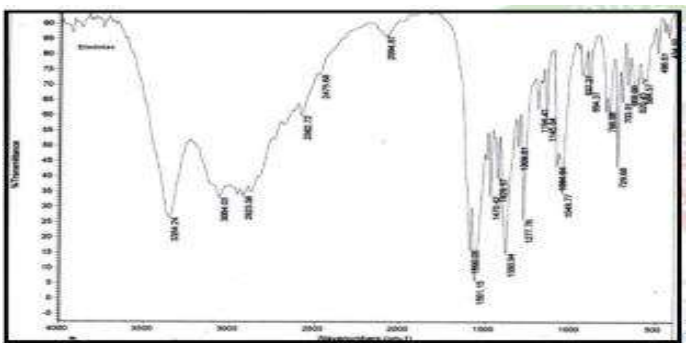


Fig-2: FTIR Spectra of physical mixture of etodolac and gellan gum

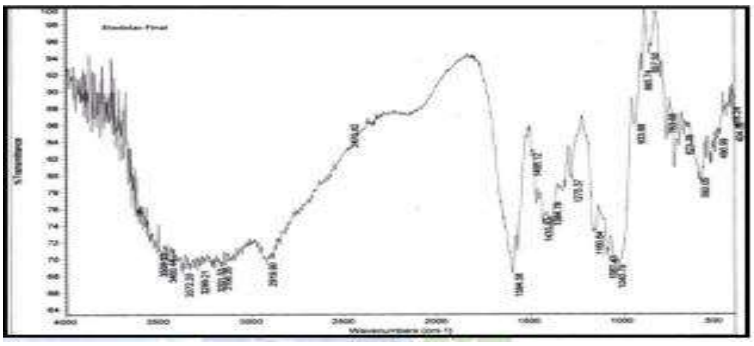


Fig-3: FTIR Spectra of physical mixture of etodolac and xanthan gum

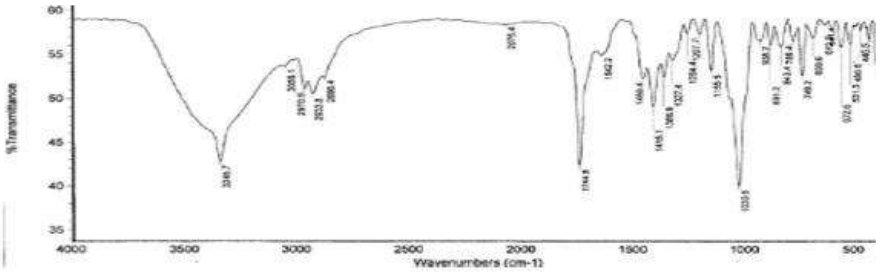


Fig-4: FTIR Spectra of physical mixture of etodolac and xyloglucan

Differential Scanning Calorimetry (DSC) analysis

The DSC thermograms for drug and physical mixture of drug and excipients are represented in figure 14 and 15 respectively. DSC analysis of Etodolac shows the exothermic peak at its melting point i.e. at 153.50C, which is in agreement of earlier observation and corresponds to the reported melting point of etodolac. The DSC analysis of physical mixture of drug and excipients revealed negligible change in the melting point of etodolac in the presence excipients. This also indicated that there are no changes in its crystallinity of the drug and it may not affect the stability of formulation and it is confirmed that drug is compatible with excipients.

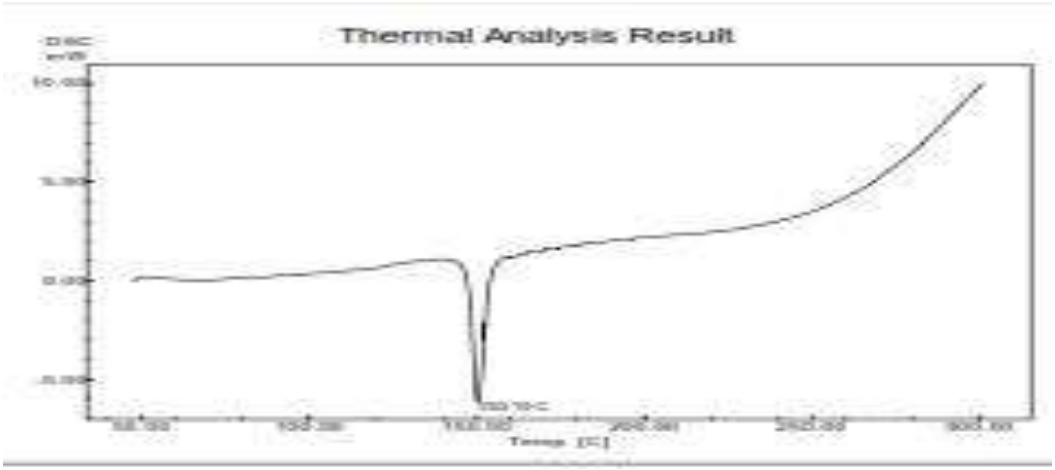


Fig-5: DSC thermogram of etodolac pure drug

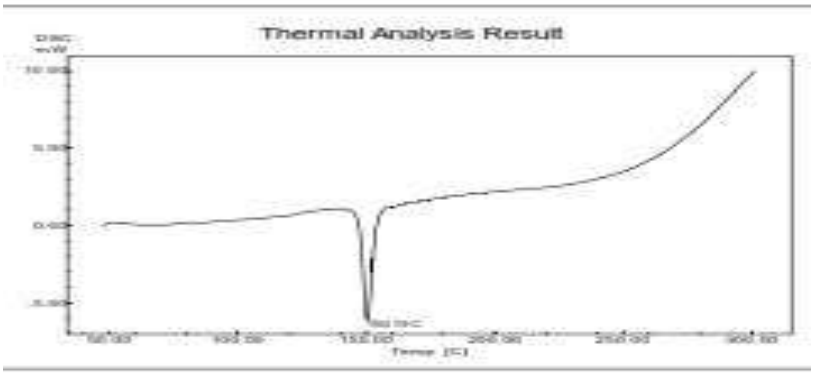


Fig-6: DSC thermogram of physical mixture of drug and different excipients

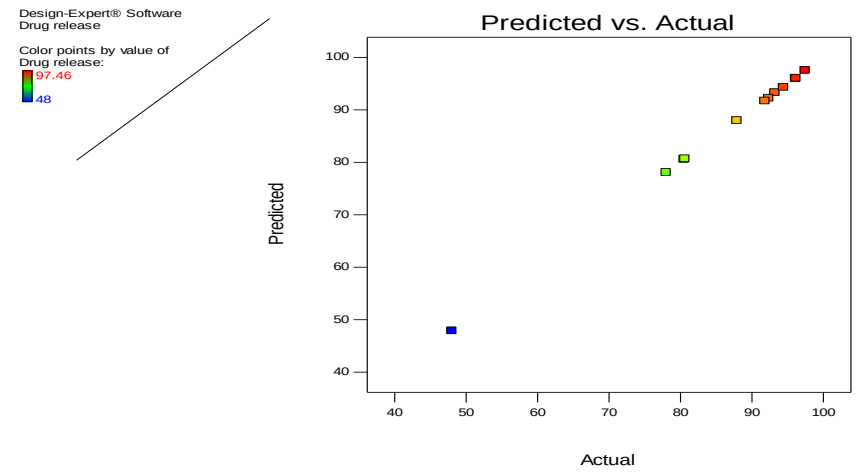
Placket-Burman Design (PBD)

PBD was carried out by considering different excipients as different independent factors at two different levels and 12 experimental runs were carried so there were 12 tablet batches using PBD from F1-F12.Statistical analysis of 12 batches in consideration with two independent factors i.e. % Drug release and Swelling index was determined.

Table-4: Analysis of variance for Drug release (DC)

ANOVA for selected factorial model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob> F	
Model	2102.76	10	210.28	1907.99	0.0178	significant
A-Gellan Gum	*8.05*	*1*	*8.05*	*73.07*	*0.0741*	
B-Sodium CMC	*142.49*	*1*	*142.49*	*1292.87*	*0.0177*	
C-Xyloglucan	*345.72*	*1*	*345.72*	*3136.97*	*0.0114*	
D-Xanthun gum	*370.63*	*1*	*370.63*	*3362.99*	*0.0110*	
E-MCC	*414.07*	*1*	*414.07*	*3757.16*	*0.0104*	
F-Talc	*251.81*	*1*	*251.81*	*2284.84*	*0.0133*	
G-Mag. Stearate	*28.99*	*1*	*28.99*	*263.00*	*0.0392*	
J-Orange flavour	*89.49*	*1*	*89.49*	*812.00*	*0.0223*	
K-Dummy factor-I	*302.91*	*1*	*302.91*	*2748.49*	*0.0121*	
L-Dummy factor-II	*148.61*	*1*	*148.61*	*1348.49*	*0.0173*	
Residual	0.11	1	0.11			
Cor Total	2102.87	11				

d.f. = degree of freedom, S = significant, NS = non-significant.
Regression coefficient (R-Squared) = 0.9999



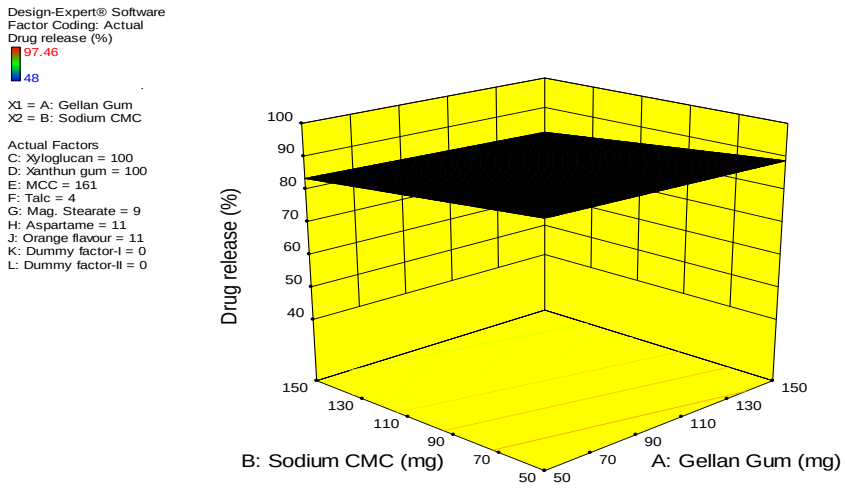
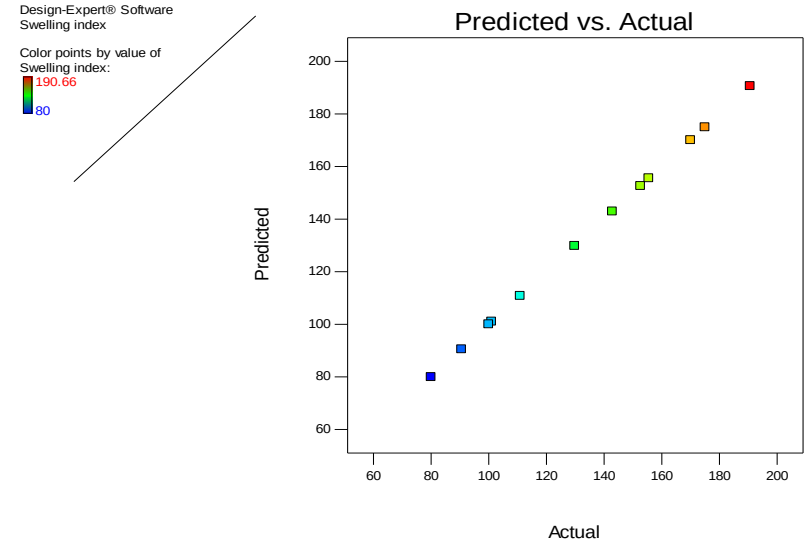


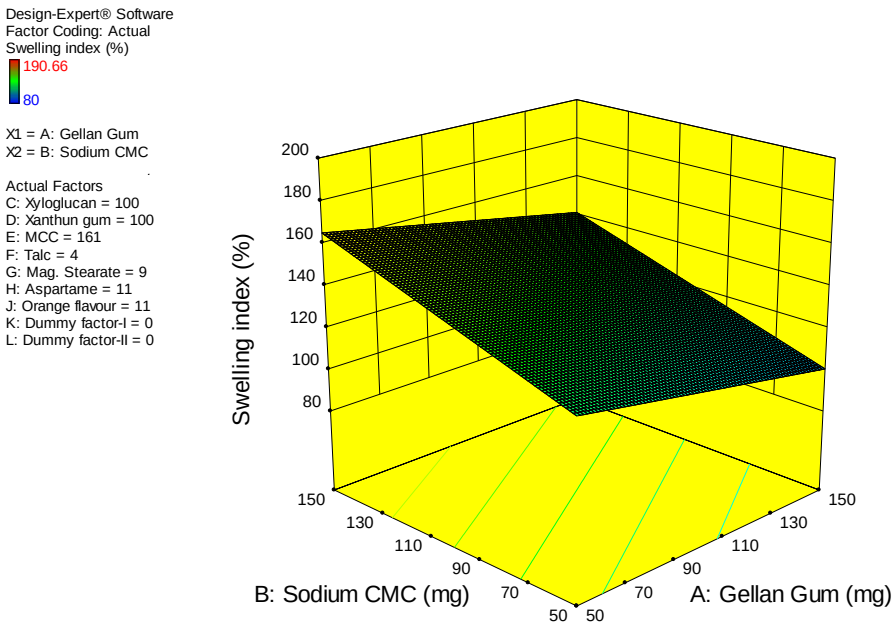
Table-5: Analysis of variance for drug Swelling Index

ANOVA for selected factorial model						
Analysis of variance table [Partial sum of squares - Type III]						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob> F	
Model	14672.40	10	1467.24	40419.84	0.0039	significant
A-Gellan Gum	*1713.15*	*1*	*1713.15*	*47194.27*	*0.0029*	
B-Sodium CMC	*5054.49*	*1*	*5054.49*	*1.392E+005*	*0.0017*	
C-Xyloglucan	*6.57*	*1*	*6.57*	*181.02*	*0.0472*	
D-Xanthun gum	*1828.29*	*1*	*1828.29*	*50366.24*	*0.0028*	
E-MCC	*34.34*	*1*	*34.34*	*946.03*	*0.0207*	
G-Mag. Stearate	*1050.94*	*1*	*1050.94*	*28951.54*	*0.0037*	
H-Aspartame	*2790.14*	*1*	*2790.14*	*76863.36*	*0.0023*	
J-Orange flavour	*9.68*	*1*	*9.68*	*266.78*	*0.0389*	
K-Dummy factor-I	*162.51*	*1*	*162.51*	*4476.83*	*0.0095*	
L-Dummy factor-II	*2022.28*	*1*	*2022.28*	*55710.30*	*0.0027*	
Residual	0.036	1	0.036			
Cor Total	14672.44	11				

d.f. = degree of freedom, S = significant, NS = non-significant.

. Regression coefficient = 0.9999; From above graphs it is clear that





Evaluation of etodolac Granules

The granules of different formulations were evaluated for angle of repose, bulk density, tapped density, Carr's index, Hausner's ratio and drug content.

Table-6: Pre compression evaluation of etodolac granules

Batches	Drug Content (%)	% Drug releases	Bulk density (gm/cm3)*	Tapped density (gm/cm3)*	Carr's index (%)*	Hausner ratio (HR)*	Angle of repose(θ)*	flowability
F1	100	110.89	0.296	0.323	8.3	1.09	32.12	Good
F2	99	90.56	0,250	0,269	7.06	1.07	31.89	Good
F3	98.33	100.99	0.260	0.290	10.34	1.11	32.49	Good
F4	99.11	99.96	0.246	0.265	7.31	1.07	31.87	Good
F5	100.44	119.78	0.276	0.300	8	1.08	34.12	Good
F6	95.75	190.66	0.289	0.337	14.39	1.16	32.87	Good
F7	96.76	173.54	0.270	0.309	12.62	1.14	32.56	Good
F8	97.77	155.5	0.269	0.305	11.80	1.13	32.56	Good
F9	96.96	142.78	0.292	0.318	8.34	1.08	33.89	Good
F10	97.97	98.65	0.268	0.317	15.45	1.18	34.1	Good
F11	94.44	155.5	0.276	0.300	8	1.08	34.12	Good
F12	89.76	152.65	0.289	0.337	14.39	1.16	32.87	Good

*All values are expressed as mean ± SD, n=3

Table 7: Post compression evaluation of etodolac tablets

Batch	Drug content (%)*	Diameter (mm)*	Thickness (mm)*	Hardness (kg/cm2) *	Friability (%)**	Weight variation (mg)***	DT(min)	Appearance
F1	100.00±4.33	10.09±0.01	3.40±0.01	7.00±0.05	0.56±0.12	498.6±1.15	ND*	++
F2	99.00±3.11	10.12±0.02	3.38±0.01	6.5±0.05	0.84±0.09	499.0±1.73	ND*	+++
F3	98.33±1.00	10.10±0.01	3.42±0.05	6.00±0.11	0.74±0.01	501.6±2.08	ND*	+
F4	99.11±2.08	10.11±0.02	3.41±0.01	7.01±0.20	0.51±0.10	501.0±3.00	ND*	++
F5	100.44±4.77	10.12±0.05	3.42±0.07	6.04±0.07	0.70±0.01	499.3±0.57	ND*	+
F6	95.75±0.88	10.06±0.03	3.39±0.01	6.75±0.74	0.81±0.16	498.0±1.00	ND*	+++
F7	96.76±1.08	10.12±0.05	3.48±0.03	6.96±0.06	0.70±0.18	498.3±1.15	ND*	++
F8	97.77±0.82	10.11±0.01	3.39±0.03	7.08±0.42	0.82±0.08	499.3±0.57	ND*	+
F9	96.96±0.30	10.13±0.06	3.41±0.05	6.52±0.04	0.56±0.08	499.0±1.00	ND*	++
F10	97.97±2.88	10.08±0.05	3.42±0.01	6.50±0.05	0.42±0.29	501.3±2.30	ND*	+
F11	94.44±4.77	10.12±0.05	3.42±0.07	6.04±0.07	0.70±0.01	499.3±0.57	ND*	+
F12	89.76±0.88	10.06±0.03	3.39±0.01	6.75±0.74	0.81±0.16	498.0±1.00	ND*	+++

*All values are expressed as mean ± SE, n=5; **all values are expressed as mean ± SE, n=10; ***all values are expressed as mean ± SE, n=20; += Average; ++= good, +++= excellent.

Swelling Behavior of etodolac matrix tablets

It was observed that as the proportion of gum in tablets increases swelling index also increased. In this batch only F5 showed optimized swelling index, which contain highest amount of gellan gum. In case of tablets containing sodium CMC and xanthan gum in different proportions showed higher swelling index as compared to other polymers.

Table-3: Swelling Index Data for Etodolac matrix tablets

Time	Run 1	Run 5	Run 11	Run 8	Run 10	Run 9	Run 3	Run 6	Run 12	Run 4	Run 2	Run 7
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
20	52.78	52.09	55.42	52.52	62.07	100.24	86.48	81.16	94.53	91.81	81.16	94.53
40	60.33	65.37	68.29	60.82	74.16	111.88	117.68	101.7	110.74	92.35	101.7	110.74
60	69.91	67.81	73.26	64.71	80.03	154.66	128.44	132.57	126.26	92.9	132.57	126.26
120	70.05	68.66	75.57	65.24	92.9	170.55	139.42	143.33	126.7	93.55	143.33	126.7
240	70.4	77.88	80.55	68.99	100.77	179.66	142	143.55	132.22	95.07	143.55	128.87
360	70.55	80.44	85.88	83.99	104.77	180.76	151.77	144.53	137.35	95.72	144.53	137.35
480	80.76	85.67	89	91.14	113.87	182.77	160.77	145.29	140.22	96.16	145.29	143.65
600	110.89	90.56	100.99	99.96	130.11	190.66	173.54	129.78	142.87	172.65	155.5	152.65

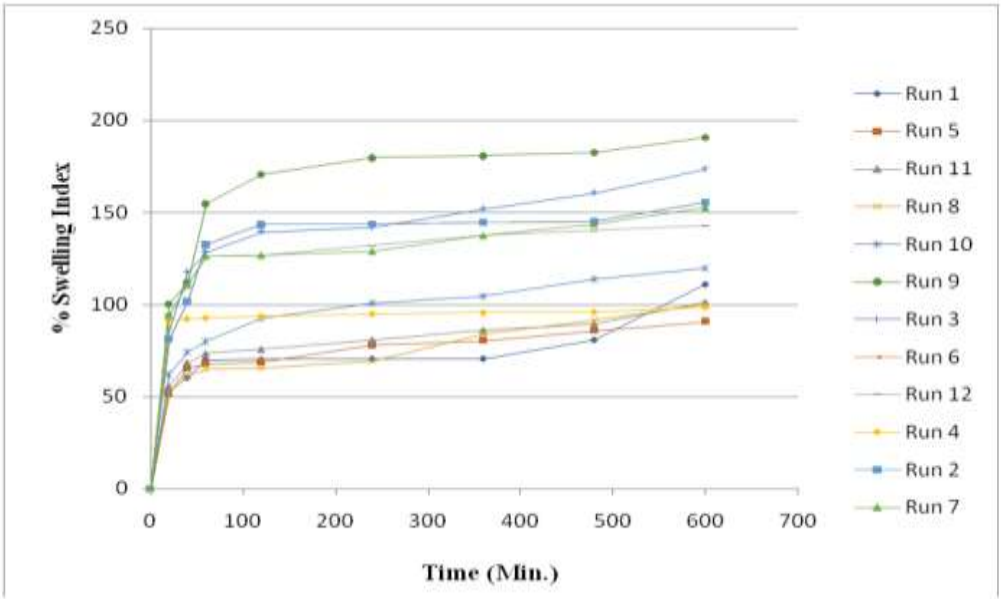


Fig-7: Swelling behaviour of different batches of etodolac matrix tablets

In vitro drug release studies

The results of *in vitro* studies indicated that the rate and extent of drug release were decreased significantly with an increase in polymer concentration, which may be attributed to increase in the polymer matrix, gel strength and to the formation of gel layer with longer path of diffusion, resulting in reduction of diffusion coefficient of the drug. When the polymer matrix tablets of etodolac come into contact with the dissolution medium, they take up water and swell, forming a gel layer around the matrix. Then the dissolved drug diffuses out of the swollen polymer matrix at a rate determined by the amount and viscosity of polymer in the tablet formulation. Microcrystalline cellulose is the most useful filler used for tablet formulations. It is water-soluble and would modify the drug release for undergoing dissolution [20-25].

Table-9: Drug release data for etodolac tablet

Time	Run 1	Run 5	Run 11	Run 8	Run 10	Run 9	Run 3	Run 6	Run 12	Run 4	Run 2	Run 7
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
0	0	0	0	0	0	0	0	0	0	0	0	0
20	52.78	79.09	89.42	14.52	90.07	77.24	76.48	91.16	84.53	91.81	88.55	88.33
40	53.33	81.37	90.29	20.82	91.16	77.68	77.68	91.7	84.74	92.35	89.2	88.98
60	56.91	86.81	91.26	25.71	92.03	78.44	78.44	92.57	86.26	92.9	89.85	89.53
120	61.7	88.66	92.57	27.24	92.9	79.09	79.42	93.33	86.7	93.55	90.29	89.85
240	63.33	89.53	93.55	28.76	94.2	79.42	79.85	93.55	87.03	95.07	90.61	91.16
360	64.09	91.48	93.98	30.17	95.5	80.29	80.39	94.53	87.35	95.72	91.37	92.13
480	65.07	92.24	94.63	30.93	96.81	80.39	80.41	95.29	87.68	96.05	91.7	93.11
600	66.26	92.35	94.42	31.15	97.46	80.5	80.61	95.5	87.9	96.16	91.81	93.22

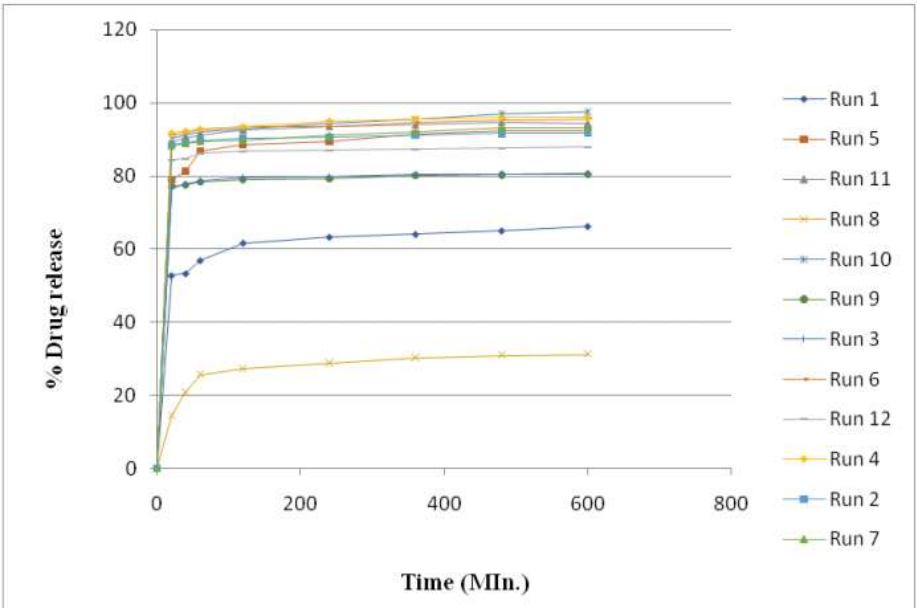
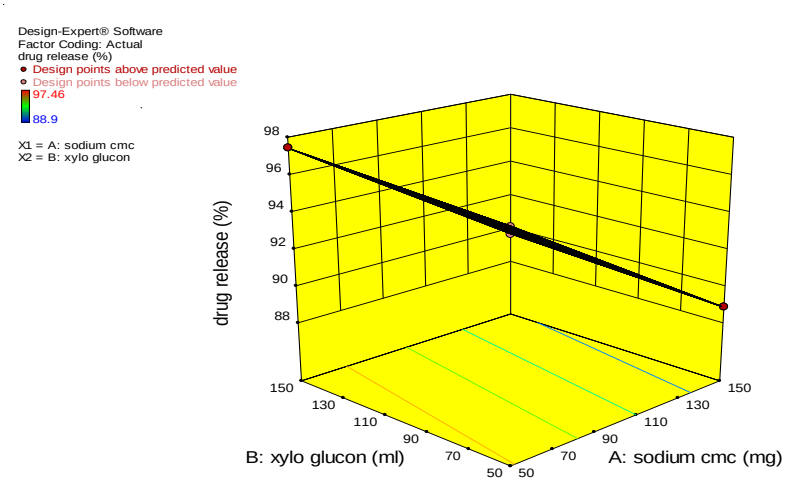


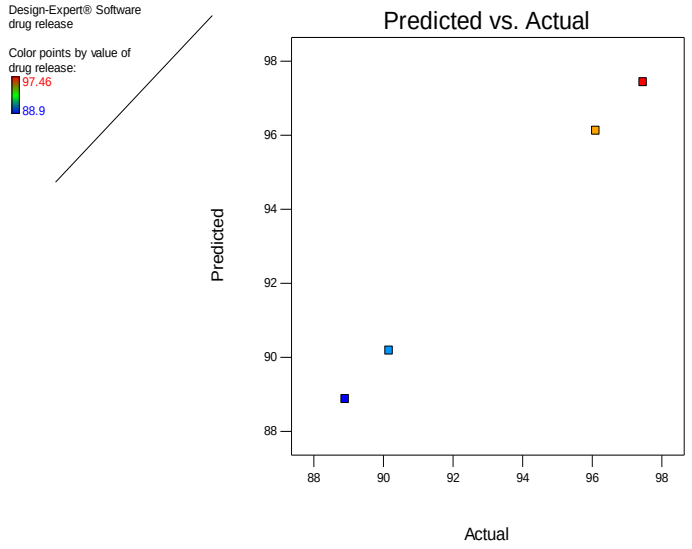
Fig-8: Comparative in vitro release profile from different batches of Etodolac matrix tablet

Factorial Design for Optimization

For drug release the p vale is found to be significant in 2^2 factorial design for both drug release and swelling index.

Analysis of variance table for % drug release						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob> F	
Model	54.28	2	27.14	10855.72	0.0068	significant
A-sodium cmc	*52.56*	*1*	*52.56*	*21025.00*	*0.0044*	
B-xyloglucon	*1.72*	*1*	*1.72*	*686.44*	*0.0243*	

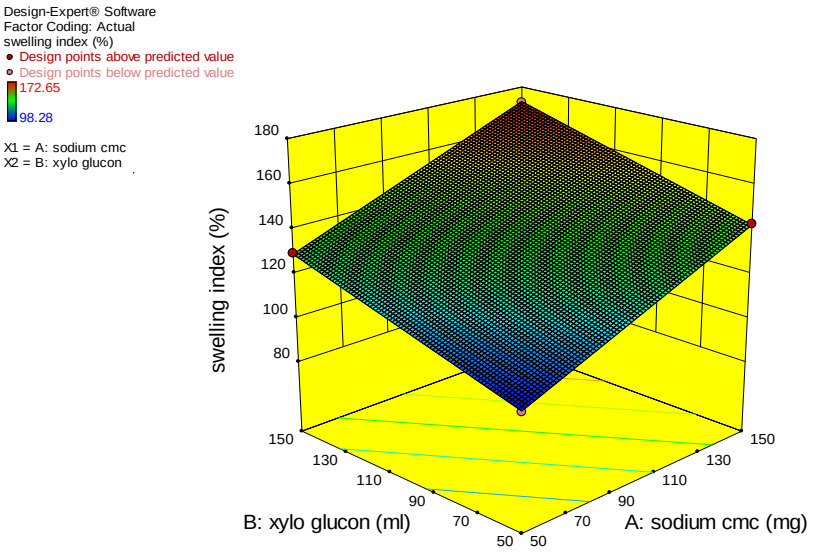


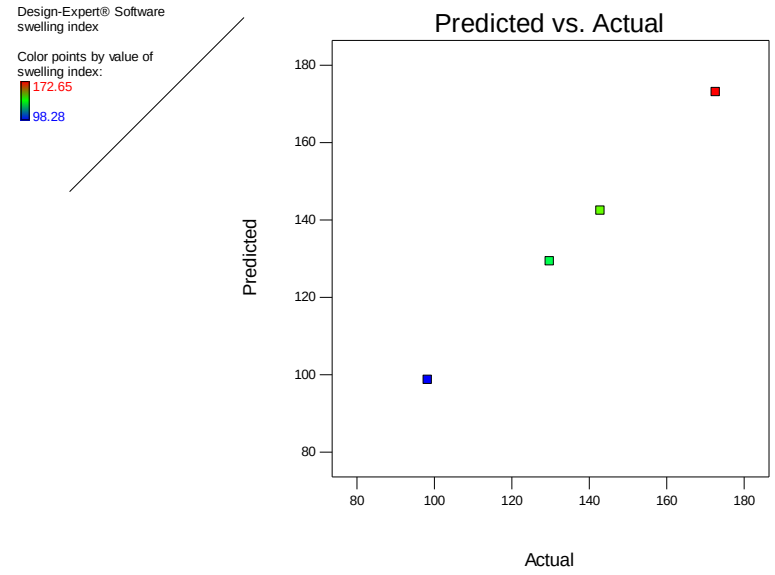


Equation of design for % drug release

Drug release= 99.09500-0.072500 (Sodium CMC) + 0.013100 (Xloglucyan)

Analysis of variance for swelling index						
	Sum of		Mean	F	p-value	
Source	Squares	df	Square	Value	Prob> F	
Model	2851.12	2	1425.56	1927.48	0.0161	significant
A-sodium cmc	*1912.31*	*1*	*1912.31*	*2585.60*	*0.0125*	
B-xyloglucon	*938.81*	*1*	*938.81*	*1269.35*	*0.0179*	





Equation of design for % drug release
Swelling Index = 61.52500+0.43730 (Sodium CMC) + 0.30640 (Xloglucyan)
From the above factorial design, the batch F5 is optimized batch.

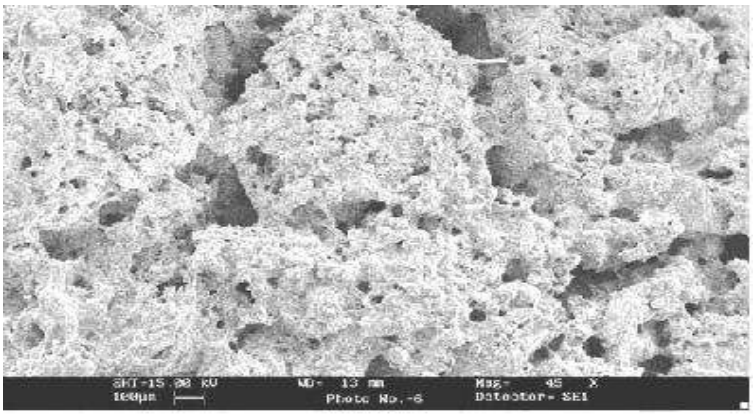


Fig-9: SEM photomicrographs of optimized batch of etodolac matrix tablet.

STABILITY STUDIES

Stability studies were conducted on optimized matrix tablet formulation (F5),no visible changes in the appearance of the matrix tablets were observed at the end of the storage period. The drug content was found to be 97.2% ± 0.70%. At the end of 12 hours of dissolution testing, the amount of etodolac released from F5 matrix tablets before storage was 99% whereas that released from the F5 formulation after storage was 97.5%. There was no significant difference in the mean amount of etodolac released from F5 matrix tablets after storing for 3 months at 40°C/75%RH, indicating that the formulation could provide a minimum shelf–life of 2 years[27-30].

Table-10: Stability study for Batch F5

	Drug Content	Drug release
Before	97.2% ± 0.70%.	99%
After	97.2% ± 0.70%.	97.5%.

CONCLUSION

In the present work, an attempt was made to develop matrix tablets of etodolac using plant based natural release retardant polymers viz: gellan gum xanthan gum, tamarind xyloglucan and sodium CMCGranules of etodolac prepared with tamarind xyloglucan, gellan gum, sodium CMC and xanthan gum were found to have good physical and flow properties'- IR spectra and DSC thermograms indicated that drug is compatible with polymers and also there were nonchemical interactions between polymers. The formulated tablets were satisfactory in terms of hardness, thickness, friability, weight variation, drug content, swelling index, and *in vitro* drug release.The drug content was uniform in all formulations ranging from 95.55 to 101.66 with lower standard deviation.

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