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Research article

Effect of polymer concentration on drug release kinetics of Etodolac

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Key words: Polymers, Drug release, Swelling Index etc.

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Abstract

Natural as well as synthetic polymers have major role in formulation as well as drug release kinetics of drugs. Polymers like gellan gum, xanthan gum, tamarind xyloglucan and sodium CMC were used in present study for formulation of etodolac tablet. Polymer concentration and combination of multiple polymers was found to be have major effect on swelling index and drug release of sustained release matrix tablet of etodolac. This effect and contribution of individual polymer in drug release and swelling index was determined using Placket Burman Design and optimized using Factorial design.

Introduction

Although oral drug dosing is the most widely accepted route of administration, the gastrointestinal (GI) tract presents several formidable barriers to drug delivery. Conventional oral drug administration does not provide rate-controlled release. New drug delivery systems (NDDS) have been successfully introduced throughout the1980s and 1990s, mainly through the development of controlled release/sustained release oral delivery forms. A sustained release dosage form is designed to maintain constant levels of a drug in the patient's blood stream by releasing the drug over an extended period. Maintaining constant blood levels of the drug in the bloodstream increases the therapeutic effectiveness of the drug. New drug delivery systems that can precisely control the release rates or target drugs to a specific body site have had an enormous impact on the healthcare system. The last two decades in the pharmaceutical industry have witnessed an avant-garde interaction among the fields of polymer and material science, resulting in the development of novel drug delivery systems. These new NDDS form were mainly applied in the therapeutic areas of cardiac disorder, arthritis, smoking cessation and chronic diseases or conditions that require continuous drug therapy for long period of time. An additional advantage of this controlled release formulation is added economic value by enhancing the patient compliance, controlled drug input that prevents super- and sub-therapeutic plasma concentration, enabling targeting of drugs to the site of action, enabling a drug's release at the time when pharmacological action is indicated/needed and increasing comfort to the patient and improving health- related quality of life [1-3].

Experimental

Material and methods

Selection of drug and polymers

Etodolac is a nonsteroidal anti-inflammatory drug (NSAID) was used in formulation to prepare sustained release matrix tablet. Gellan gum is a water-soluble anionic polysaccharide produced by the bacterium *Sphingomonas elodea* (formerly *Pseudomonas elodea*) was used in the formulations. The isolation of Xyloglucan was performed by following the method reported earlier. 20 g of tamarind kernel powder was added to 200 ml of cold distilled water to prepare slurry. The slurry was poured into 800 ml of boiling distilled water. The solution was boiled for 20 min with continuous stirring. The resulting solution was kept overnight and centrifuged at 5000 rpm for 20 min. The supernatant liquid was separated and poured into twice the volume of absolute alcohol with continuous stirring. The precipitate obtained was washed with absolute ethanol and air-dried. The dried polymer was milled, passed through sieve no. 85 and stored in desiccators until further use.

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, 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}.

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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 design using polymers

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.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. (Table 1 and 2). Drug concentration of etodolac was 200 mg per tablet.

Table 1. Excipients / Factors for Placket Burman Design (PBD)

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

Table 2. Experimental batches according to Placket Burman Design

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

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

Tablets were prepared by wet granulation method using formulas of different experimental batches.

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 [3-5].

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 [6-8].

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 12th hour of dissolution. The morphological characters of these 2 scans were compared to hypothesize the mechanism of drug release and swelling [9-12].

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 [13-16].

Result & Discussion

Fourier transform infrared (FTIR) spectral analysis

Physical mixture of etodolac and formulative 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 formulative ingredients were depicted in figure 1, 2 and 3.

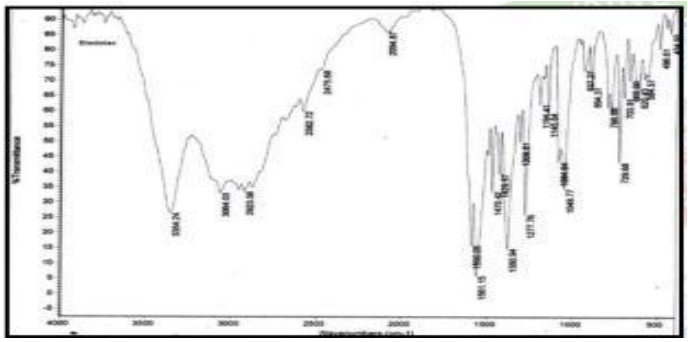


Figure 1. FTIR Spectra of physical mixture of etodolac and gellan gum.

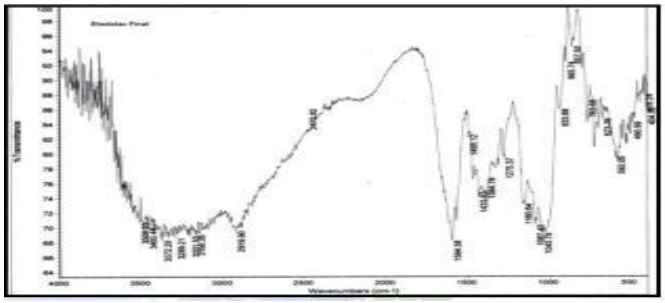


Figure 2. FTIR Spectra of physical mixture of etodolac and xanthan gum.

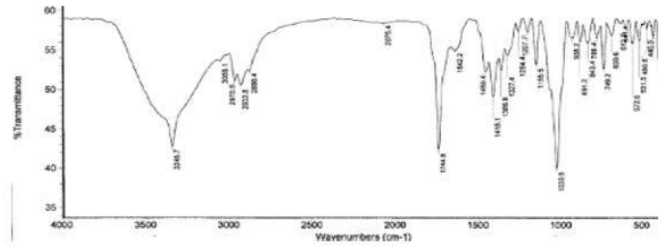


Figure 3. FTIR Spectra of physical mixture of etodolac and xyloglucan

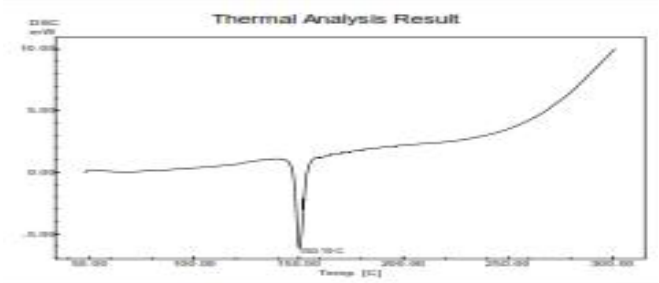


Figure 4. DSC thermogram of etodolac pure drug.

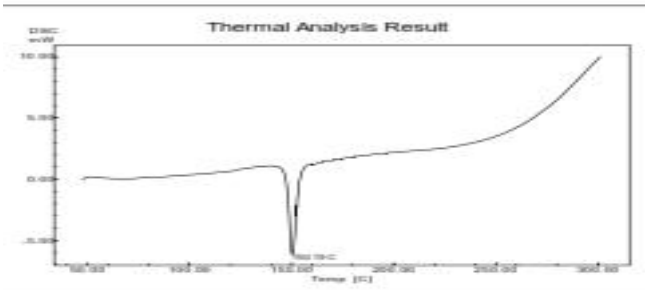


Figure 5. DSC thermogram of physical mixture of drug and different excipients.

Differential Scanning Calorimetry (DSC) analysis

The DSC thermograms for drug and physical mixture of drug and excipients are represented in figure 4 and 5 respectively. DSC analysis of Etodolac shows the exothermic peak at its melting point i.e. at 153.5°C, 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.

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 3) and graphically it is represented in figure 6, 7, 8, 9.

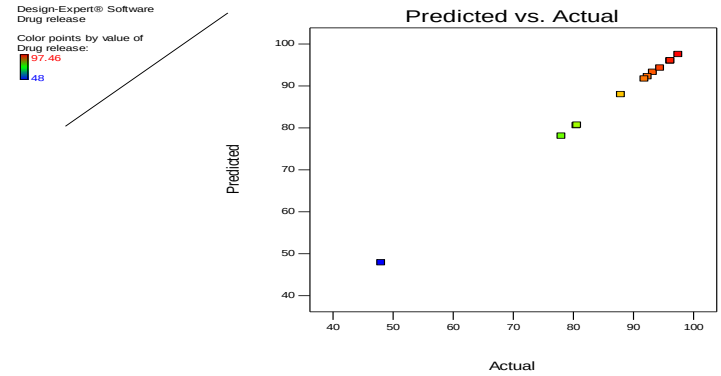


Figure 6. Predicted vs. Actual % Drug release by PBD in Graphical.

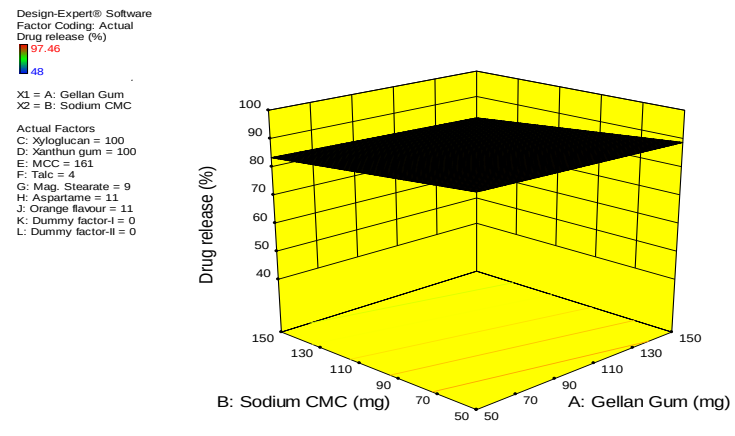


Figure 7. % Drug release by PBD in Graphical.

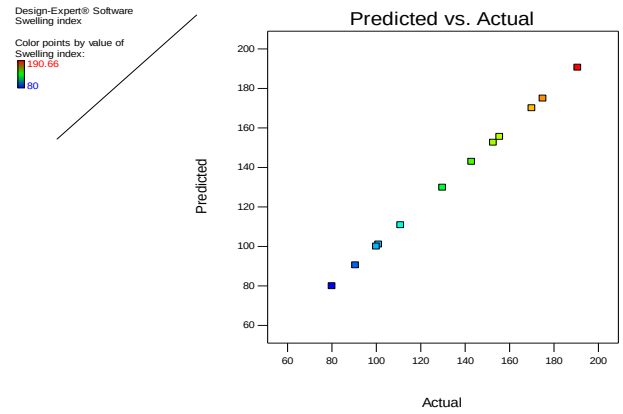


Figure 8. Predicted vs. Actual % Swelling Index by PBD in Graphical.

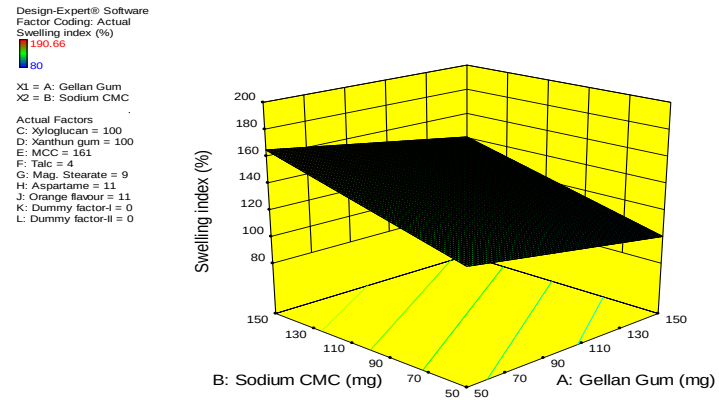


Figure 9. % Swelling Index by PBD in Graphical.

Table 3. Analysis of variance for Drug release (%DR)

ANOVA for Placket Burman Design (PBD)
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-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				

Table 4. Analysis of variance for drug Swelling Index

ANOVA for Placket Burman Design (PBD)
Analysis of variance table [Partial sum of squares - Type III]

Source	Sum of Squares	df	Mean Square	F Value	p-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				

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 4) comparative graph for different runs is shown in figure 10.

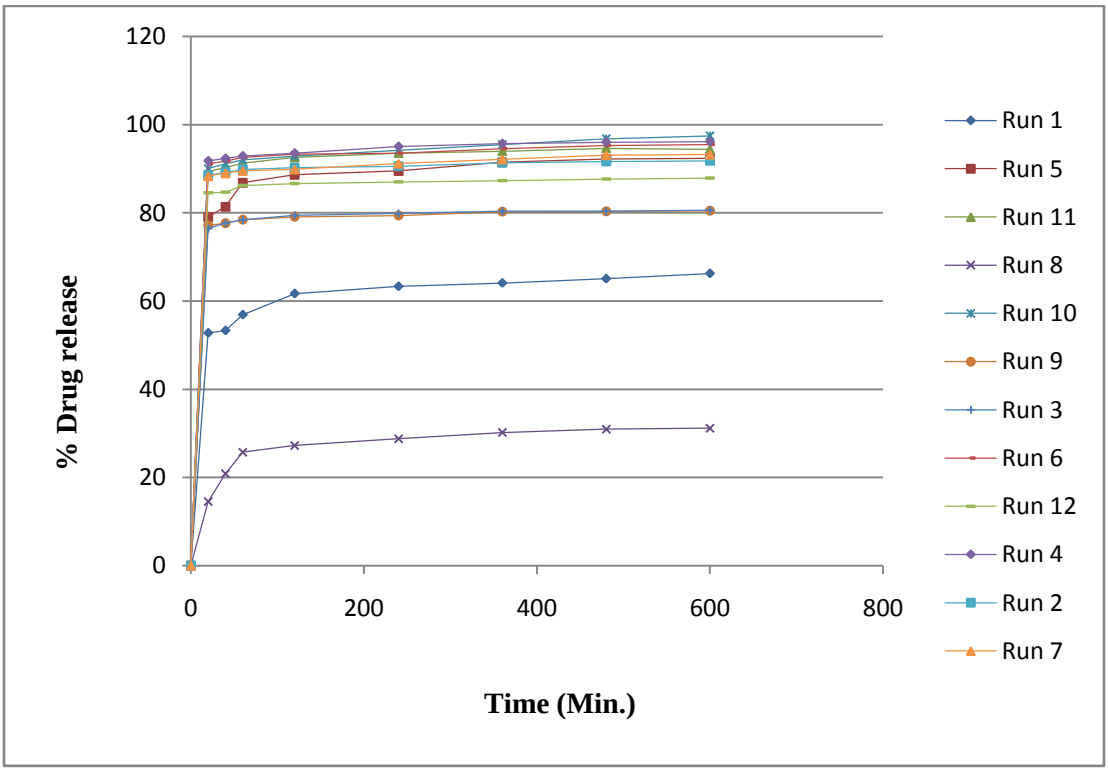


Figure 10. Comparative in vitro release profile from different batches of Etodolac matrix tablet

***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, (Table 5) 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. Comparative drug release for different runs is shown in figure 11. 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. (Table 6). Microcrystalline cellulose is the most useful filler used for tablet formulations. It is water-soluble and would modify the drug release for undergoing dissolution [17-20].

Table 5. Drug release data for etodolac tablet

Time	Run 1 F1	Run 5 F2	Run 11 F3	Run 8 F4	Run 10 F5	Run 9 F6	Run 3 F7	Run 6 F8	Run 12 F9	Run 4 F10	Run 2 F11	Run 7 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

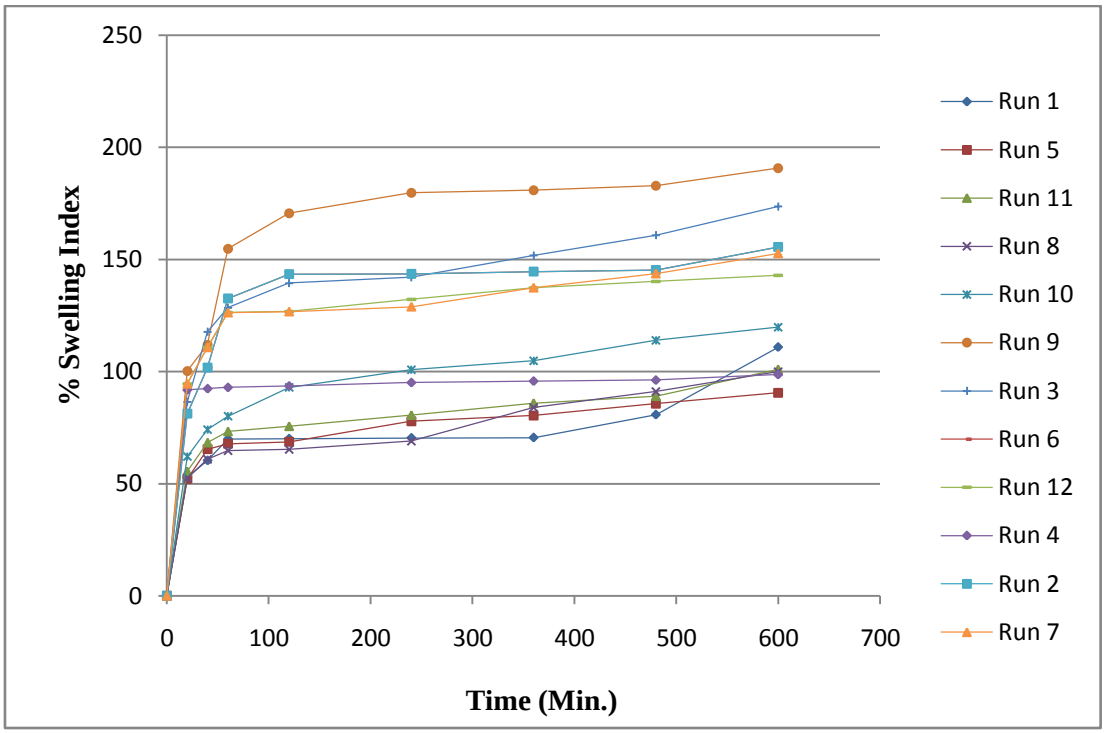


Figure 11. Swelling behaviour of different batches of etodolac matrix tablets.

Table 6. Swelling Index Data for Etodolac matrix tablets

Time	Run 1 F1	Run 5 F2	Run 11 F3	Run 8 F4	Run 10 F5	Run 9 F6	Run 3 F7	Run 6 F8	Run 12 F9	Run 4 F10	Run 2 F11	Run 7 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

Scanning electron microscope

The surface morphology of optimized formulation (F10) at zero time and at 12th hour of dissolution study was observed. SEM photographs before dissolution it showed intact surface without any perforations, channels, or troughs. After dissolution, the solvent front enters the matrix and moves slowly toward the centre of the tablet. The drug diffuses out of the matrix after it comes in contact with dissolution medium. The images of the tablet showed the presence of both gelling structures and pores on the surface. Thus, the presence of both pores and gelling structure indicates the combination of diffusion and erosion mechanism in the release of etodolac from the matrix tablet of batch F10. The SEM photographs of etodolac matrix tablet (F10) were shown in Figure 12.

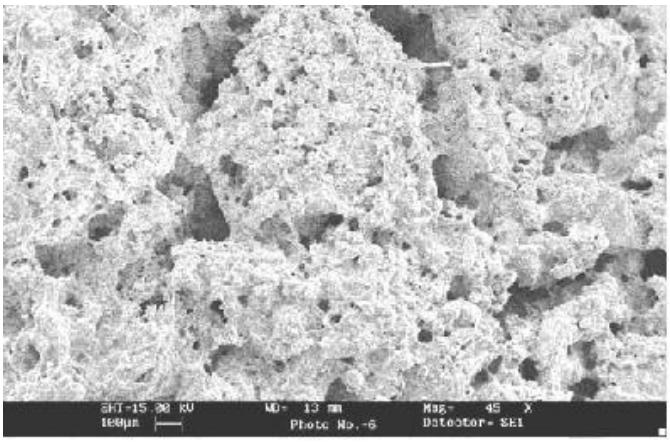


Figure 12. SEM photomicrographs of optimized batch of etodolac matrix tablet.

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 (Table 7 and 8) Equation of design for % drug release

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

Equation of design for % drug release

Swelling Index = 61.52500+0.43730 (Sodium CMC) + 0.30640 (Xyloglucan)

From the above factorial design, the batch F5 is optimized batch and this optimization is shown graphically in figure no. 13, 14, 15, 16.

Table 7. Analysis of variance for Drug release (% DR)

Analysis of variance table for % drug release for optimization						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-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	

Table 8. Analysis of variance for Drug release (% DR)

Analysis of variance for swelling index for optimization						
Source	**Sum of Squares**	**df**	**Mean Square**	**F Value**	**p-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	

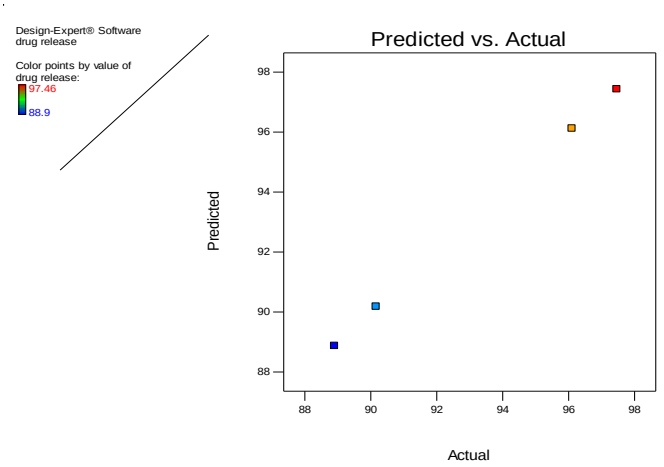


Figure 13. Predicted vs. Actual % Drug release optimization in Graphical.

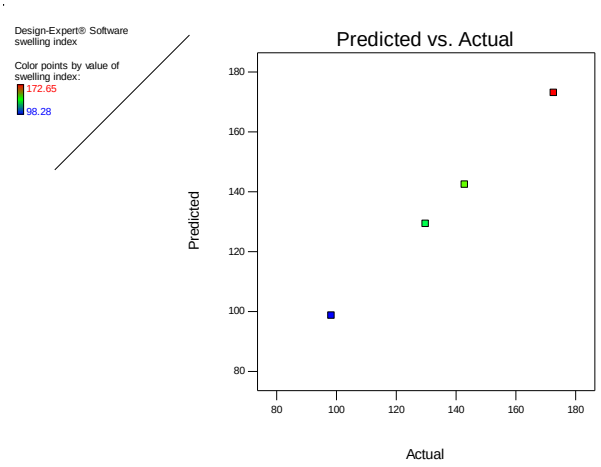


Figure 15. Predicted vs. Actual % Swelling Index optimization in Graphical.

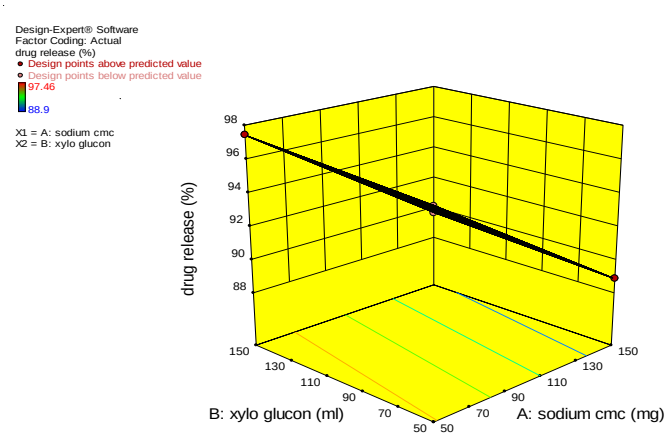


Figure 14. % Drug release optimization graphical

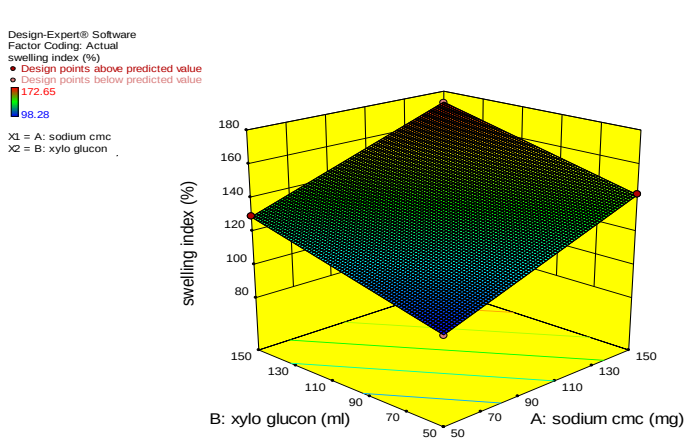


Figure 16. % Swelling index optimization graphical.

Conclusion

During this study, it was also found that drug**:** polymer concentration ratio influences the drug release behaviour. As the concentration of the polymer increased in the tablet the swelling index also increased. Tablets containing xanthan gum and sodium CMC showed highest swelling index. It was observed that as the concentration of the polymer in the tablet increased the rate of drug release form the tablet was retargetable formulation containing xanthan gum (F5) was considered the optimized batch. Formulation F5 was found to be the best on the basis of, swelling study and *in vitro* drug release and it was found that Sodium CMC and Xyloglucan have major contribution in drug release kinetics.

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