DEVELOP & EVALUATE THE NOVEL S.R. MATRIX FORMER BY PHYSICAL & CHEMICAL MODIFICATION OF OKRA POLYSACCHARIDE

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ABSTRACT:
The aim of this research work was to Natural Polysaccharide used as SR Matrix Tablet, any pharmaceutical formulation contains two ingredients one is the active ingredient and other is an excipients. In current senario, various plant have been studied for their diverse applications as excipients like binders, granulating agents, disintegrants, emulsifiers, suspending agents, gelling agents, mucoadhesive agents, matrix-formers, release retardants, enteric resistant, etc., in various pharmaceutical dosage forms. Among these, okra mucilage is an emerging excipient the current chapter deals with a comprehensive and useful discussion on extraction & isolation, chemical composition and properties of okra mucilage. Okra modification was done successfully by physical as well as chemical modification methods. Among these chemical modifications was found to be best possible method for formulation of SR matrix former. Drug-polymer compatibility study by IR Spectroscopy, which proves that there were no any chemical interactions.An excipients help in the manufacturing of dosage form and it also improves physicochemical parameters of the dosage form The main objective of the present study was to develop, formulate and evaluate a matrix tablet by using hydrophilic natural retardant polymers which would retard drug release in upper GI tract and should start releasing the drug when it reaches the alkaline environment of small intestine. Okara were investigated as the model hydrophilic retardant polymers. The prepared tablets were subjected for pharmacopoeial and non-pharmacopoeial evaluation parameters including loose and tapped bulk density, compressibility index, hausner ratio, angle of repose, friability, hardness, thickness, weight variation, % drug content and in-vitro drug release studies. It can be concluded that the combination of hydrophilic polymers that are retardant in nature are better suited for sustained and controlled drug delivery system than the hydrophilic polymer alone.

KeyWords: Polymer, Sustained Release, Okra,

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INTRODUCTION:

Sustain release provides most desirable dosing regimen and it alleviate the variability involved in the administration of multiple doses per day. Simple definition of sustained release drug system is "any drug or dosage form modification that prolongs the therapeutic activity of the drug" called as sustain release drug system.. Ideally a sustained release oral dosage form is designed to release rapidly some pre-determined fraction of the total dose (loading dose) is an amount of drug, which will produce the desired pharmacological response as promptly as possible and the remaining fraction of the total dose (maintenance dose) is then release at a constant rate. The rate of the drug absorption from the entire maintenance dose into the body should equal to the rate of the drug removal from the body by all the processes over the time for which the desired intensity of pharmacological response is required.

In recent years, natural polysaccharides are growing rapidly importance in the new formulation development of the controlled released dosage form as they are much safer than synthetic. Interest in gums and mucilage's used in pharmaceutical industry as an excipient in various formulations for various roles such as binder, matrix former, emulsifying agent, suspending agent, floating agent, Mucoadhesive etc.

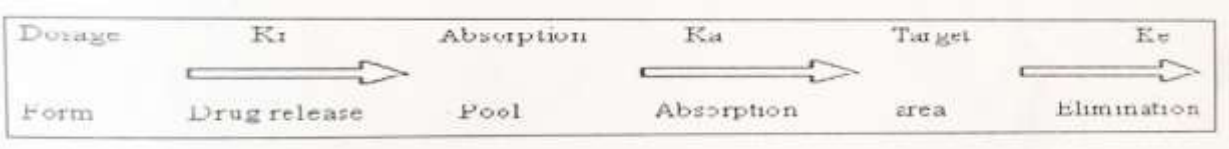
Ideally two main objectives exist for these systems:

1) **Spatial** drug delivery, which is related to the control over the location of drug release.

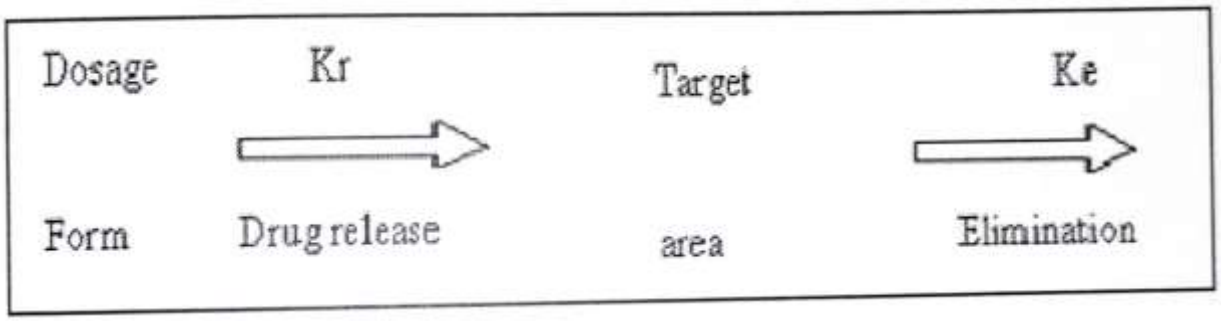
2) **Temporal** drug delivery, in which the drug is delivered over an extended period of time during treatment (Vyas SP & Khar RK. 2002)

Principle of Sustained Release Drug Delivery

The conventional dosage forms release their active ingredients into an absorption pool immediately. This is illustrated in the following simple kinetic scheme.



The absorption pool represents a solution of the drug at the site of absorption, and the term Kr, Ka and Ke are first order rate-constant for drug release, absorption and overall elimination respectively. Immediate drug release from a conventional dosage form implies that Kr>>>>Ka. Alternatively speaking the absorption of drug across a biological membrane is the rate-limiting step. For non-immediate release dosage forms, Kr<<<Ka i.e. the release of drug from the dosage form is the rate limiting step. This causes the above Kinetic scheme to reduce to the following.



Essentially, the absorptive phase of the kinetic scheme become insignificant compared to the drug release phase. Thus, the effort to develop a non-immediate release delivery Drug release system must be directed primarily at altering the release rate.

Materials & Methods

Diclofenac Sodium was obtained as a gift sample from Wockhardt Limitd,Aurangabad and other ingredients like okra were isolated & extracted was carried out at laboratory (Pharmaceutics Research lab) Pune, other Excipients Ethanol, Thionil Chloride, Phenyl acetic acid, acetone, sodium hydroxide, SD fine chemical.

Table 1. FORMULATIONS OF OKRA & HPMC TABLETS

Ingredients.	**Quantity (mg)**										
Formulation	**F1**	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**	**F11**
Diclofenac Sodium	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**	**100**
Okra	**20**	**40**	**60**	**80**	**100**	-	-	-	-	-	-
HPMC(K100)	-	-	-	-	-	**60**	**100**	-	-	-	-
HPMC(K4M)	-	-	-	-	-	-	-	**60**	**100**	-	-
HPMC(K15M)	-	-	-	-	-	-	-	-	-	**60**	**100**
MCC	**122.5**	**102.5**	**82.5**		**42.5**	**82.5**	**42.5**	**82.5**	**42.5**	**82.5**	**42.5**
Mg-Stearate 3%	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**	**7.5**
Total wt.	**250**										

PROCEDURE-

Above table shown formulation specifications The (Drug:Okra) polymer ratio was taken 1:0.2,1:0.4,1:0.6,1:0.8,1:1 and formulation code was given F1,F2,F3, F4,F5 respectively. Drug and all other excipients were passesed through a 100# sieve. Weighted accurately as stated in above formulation, Mix all ingredient and drug in a poly bag except mg-stearate; add 1% PVP K-30 solution as granulating agent to form a damp mass of above mixture. Damp mass was passed through mesh No. 18. #, the we granules were dried at 40°C. The dried granules were sized by mesh No. 25# and mixe with magnesium stearate, formulation blend were compressed by using karnavati mul punch tableting machine having punch size 8.5 mm. Total weight of tablet was 250 m All formulation was prepared. Formulated tablets were stored in desiccators in s sealing punch and were withdraw successfully for the evaluation.

Various Modification Methods Selected for Okra Polysaccharides:

1. Physical Modifications

1) Microwave Technique
2) Addition of carbopol

2. Chemical Modifications (Acetylation of Okra polysaccharide)

1) Acetyl chloride
2) Phenyl acetyl chloride
3) Method A
4) Method B
5) Method C

Microwave Technique:

Accurately weighed 1gm of pure Okra and deionized water (Iml) were mixed until the Okra was hydrated. That mixer was poured in a lidless glass petridish and entire mass was exposed to a microwave at 700W for various time intervals (3,5,7 and 10) min. Dried material (Modified

Okra) was collected, passed through a sieve 100# and stored in a desiccator for further study. Formulated the tablets by using microwave modified Okra and evaluated for hardness, swelling ratio, friability, % drug release from formulation.

2 Addition of Carbopol 971P: (Chikhlikar kedar 2009) Carbopol Ⓡ polymers are polymers of acrylic acid cross linked with either allyl ethers of sucrose or pentaerythritol. Lubrizol scientists have prepared a number of OSD formulations on as a hydrogel matrix modified release ingredient as well as to add secondary physical and delivery benefits such as improved binding, taste masking, and bioadhesion. The paper "An Investigation into the effect of Carbopol Ⓡ polymers on the release of Propranolol HCI from tablet matrices" describes wet granulation of Propranolol blends and various carbomer grades using solution of Povidone in Chloroform as granulating agent. (Mortazavi et al, 2003), Nifedipine ER tablets using Carbopol® 971P NF is presented in Lubrizol's patent 2004219210 Nifedipine ER Tablets 30 mg, Metformin HCI SR Tablets 500 mg and 1000 mg, have been developed in Lubrizol laboratories using the non aqueous granulation technique. In the process of Aqueous wet granulation, the powder grades of Carbopol@ polymers are recommended such as Carbopol® 971P NF, Carbopol® 974P NF. The recommended levels are 5 to 10 percent.

Table 2.: Formulation of M Okra (Microwave) tablet

Ingredients	Quantity (mg)				
formulation	MI	M2 (3min)	M3 (5min)	M4 (7min)	M5 (10min)
Drug	100	100	100	100	100
M.Okra	100	100	100	100	100
MCC	42.5	42.5	42.5	42.5	42.5
Mg.stearate	7.5	7.5	7.5	7.5	7.5
Total wt.	250				

Note: M- Modification of Okra polysaccharide by microwave technique

Table 3. : Formulation of Okra Tablet by use of Carbopol 971p

Ingredients	Quantity (mg)				
Formulation	C1(1%)	C2(2%)	C3(5%)	C4(7%)	C5(10%)
Drug	100	100	100	100	100
Okra	100	100	100	100	100
Carbopol	2.5	5	12.5	17.5	25
MCC	40	37.5	30	25	17.5
Mg.stearate	7.5	7.5	7.5	7.5	7.5
Total wt.	250				

*Note: C-Modification by addition of carbopol 971p.

2. Chemical Modification Methods:

1 Using Acetyl chloride (Ac): (Manish Bhatia et al 2008) 1) Product1: 10gm Okra in flask placed on magnetic stirrer. Freshly prepared 40% v/v acetyl chloride in ethanol was transferred into burette and 5 ml were added drop wise under stirring over a period of 30 min. The product was washed with water, filtered and dried in a hot air oven at 37 °C.

2) Product2: 10 gm Okra was gradually added into a flask containing 5 ml of freshly prepared 40% v/v acetyl chloride in ethanol over a period of 90 min. The product was filtered, washed and dried in a hot air oven at 37 °C.

1. IR Spectroscopy:

The finger print region of the spectrum consist of two character peaks between 700 and 1316 per cm attributed of the C-O bond stretching The band at 1059 per cm was assigned to the O-H bending in secondary hydroxyl of water, Contribution from carbonyl stretching in region of 1700 cm indicate ester linkages. At 1637cm show the C=O streaching, Weak stretching in the region of 1650-1690cm indicates presences of lignin. At 1039cm cm' etherical linkages are observed which are aromatic as well as aliphatic type. The sharp band at 3140.51 per cm is characteristic of methyl C-H stretching associated with aromatic ring the broad band at 3396 cm" is due to the hydrogen bonding that contribute to the complex Vibration stretching associated with free inter and intra-molecular bound hydroxyl group which make up the gross structure of carbohydrate this is all consist with a polysaccharide structure that is neither a starch nor a cellulose but doesn't have some peptide crosslinkage. The IR spectrum is shown in **Figure 6.1.**

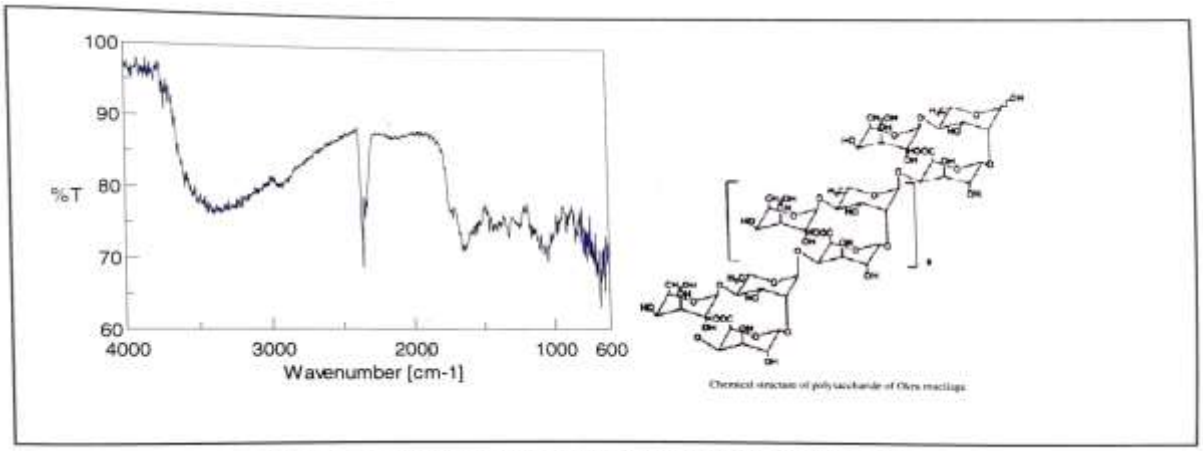


Figure 6.1: IR spectrum of *Okra* polysaccharide

Table 4: Characteristic peaks of Okra polysaccharide powder

Functional group	Characteristic peak (cm)	Obtained peak (cm)
O-H (Broad peak)	3600-3200	3396
C-C (Stretching)	1300-800 (Weak band)	840.81
C-O-C	700-1316	1039.44
C=O Stretching	1600-1700	1637.27
Sec.-OH(Bending)	1100-1050	1059

2. Differential Scanning Calorimetry (DSC):

Differential scanning calorimetry (DSC) was used to measure the occurrence of exothermal or endothermal changes with increase in temperature. DSC, because of its sensitivity and accuracy, has been extensively used to study the phase transitions of polymers. The thermogram of Okra shown in Figure 6.2, as the thermogram show endothermic peak so, Okra powder has amorphous nature. Glass transition (Tg) temperature occurred at 54.9° C and the corresponding parameters.

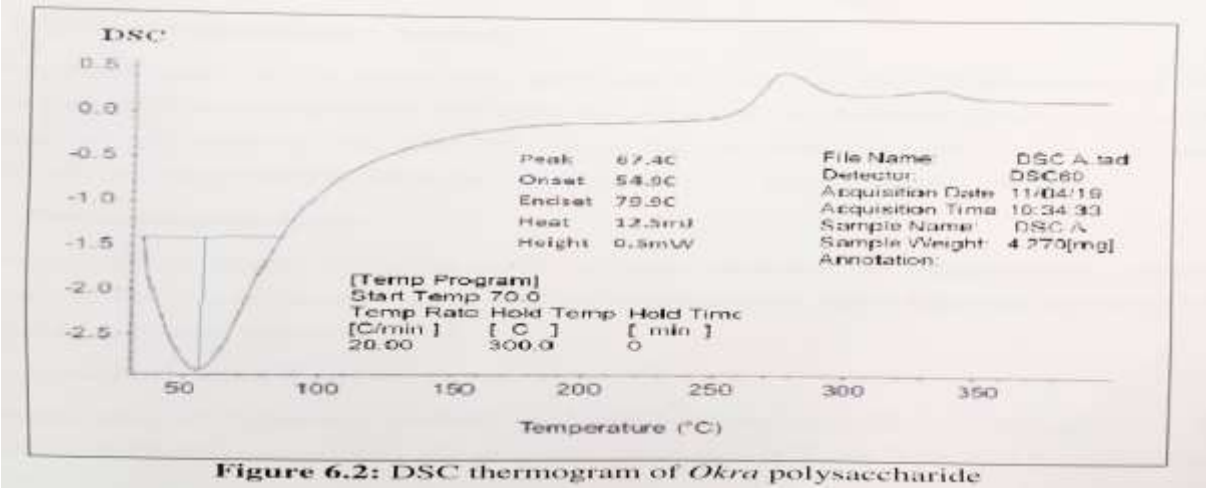


Figure 6.2: DSC thermogram of *Okra* polysaccharide

Table 5.: Thermal parameter of Okra polysaccharide

Sr. no.	Parameter	Result
1	Onset temperature (°C)	54.9°C
2	Peak temperature (°C)	67.4° C
3	End set temperature (°C)	79.9°C

3. Nuclear Magnetic Resonance (NMR) Analysis:

Okra was insoluble in DMSO-d6, hence spectrum of 1H NMR was not obtained.

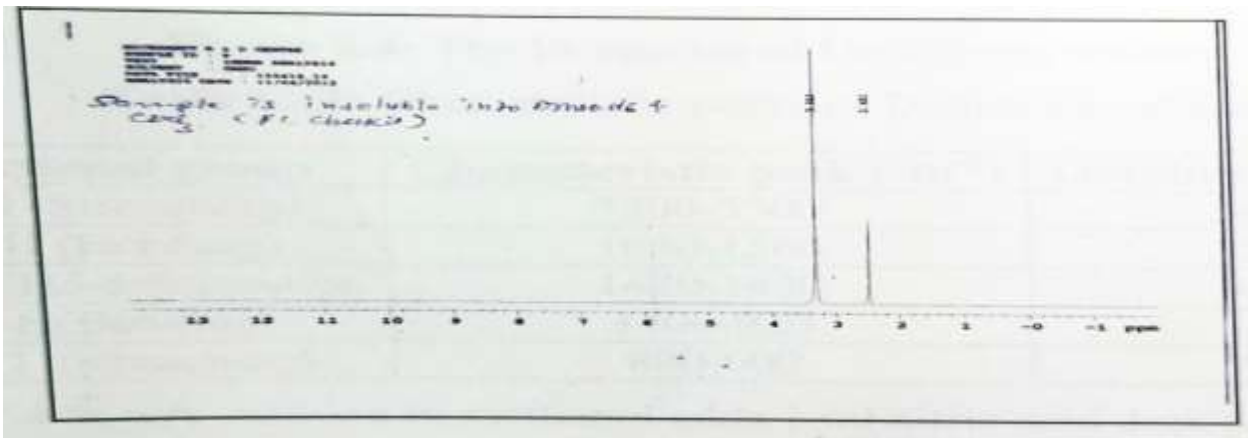


Figure 6.3: NMR of Okra polysaccharide

4. UV Spectrophotometry Analysis:
Ultraviolet and visible absorption spectrophotometry is the measurement of the absorption of monochromatic radiation by solutions of chemical substances, in the range of (185-380) nm and (380-780) nm of the spectrum, respectively. Okra powder solution (in water) did not show any absorption in UV range (i.e. 185-780) nm)

5. Preformulation Study
Preformulation studies including purity of drug candidate, its identification, melting point, solubility, calibration curve and the compatibility study between the drug and selected polymers were evaluated.

Identification Test (A)
Identification of Diclofenac sodium was performed by using IR spectroscopy The IR spectra of Diclofenac sodium shows peaks as shown in Table 6.13 (Terry mills et al. 2006)

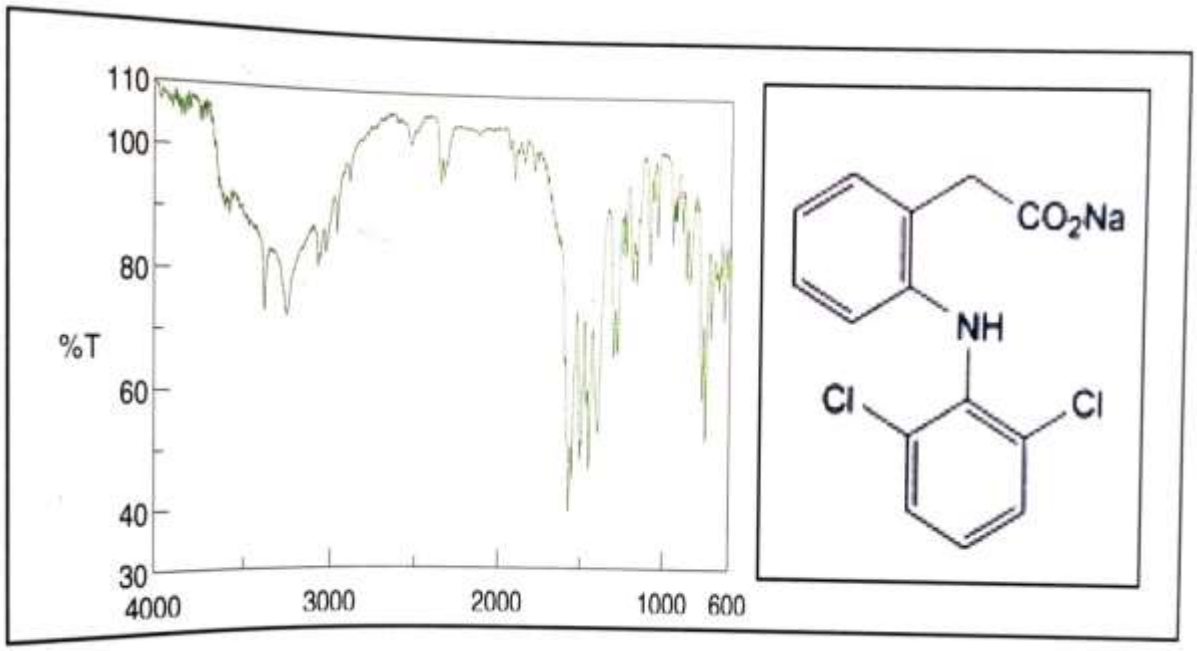


Figure 4: The IR spectra of Diclofenac sodium

Table 6: Characteristic peaks of Diclofenac sodium

Functional group	Characteristic peak (cm)	Obtained peak (cm)
N-H (Streaching)	3300-3500	3430.59
NH (Bending)	1650-1560	1575.56
CH2CH3 deformation	1470-1430	1452.57
O-H(Bending)	1400-920	1400.7
C-CI (streaching)	800-600	747.28

(B) 1 ml of 4% w/v solution in methanol adds I ml nitric acid dark red colour obtained confirmation of Diclofenac sodium.

2. Melting Point
The melting point of the Diclofenac sodium was found to be in the range of 276-280°C.

3.Solubility of Diclofenac sodium
The solubility of Diclofenac sodium was found to be 0.885 mg/ml.

4. Construction of calibration curve of Diclofenac sodium
UV scans of Diclofenac sodium shown the absorption maxima at wavelength 276 mm and it is shown in **Figure 6.5**

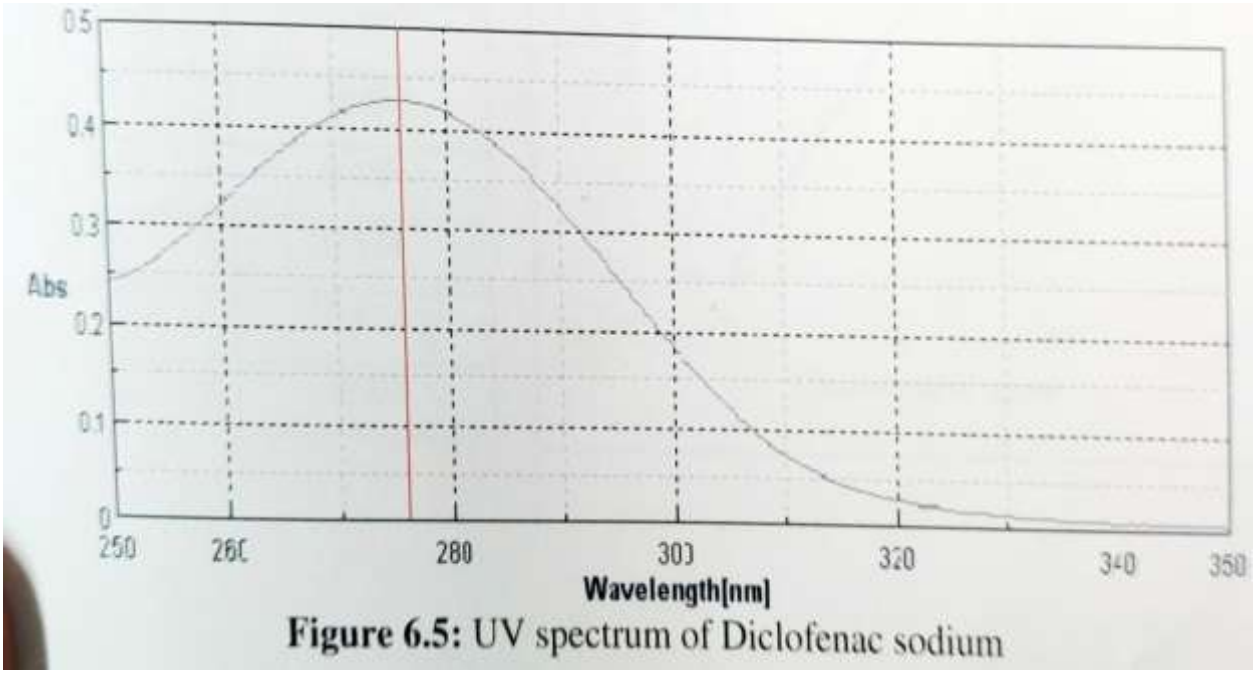
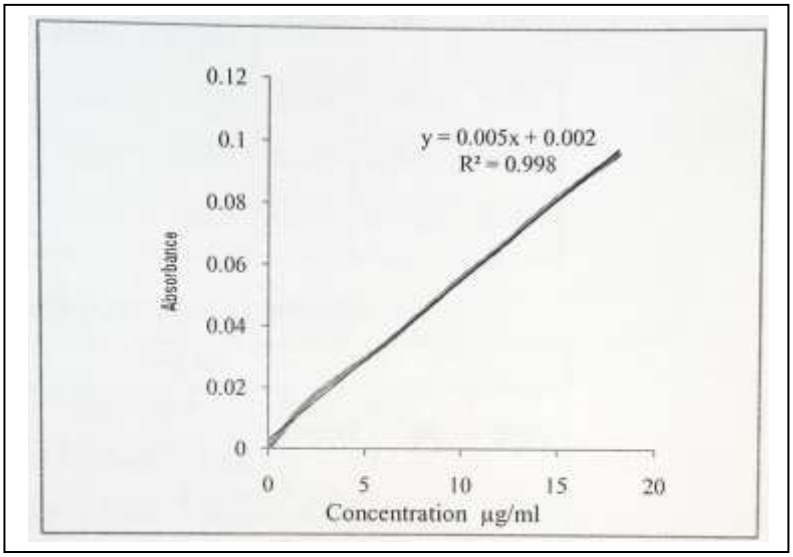


Figure 6.5: UV spectrum of Diclofenac sodium

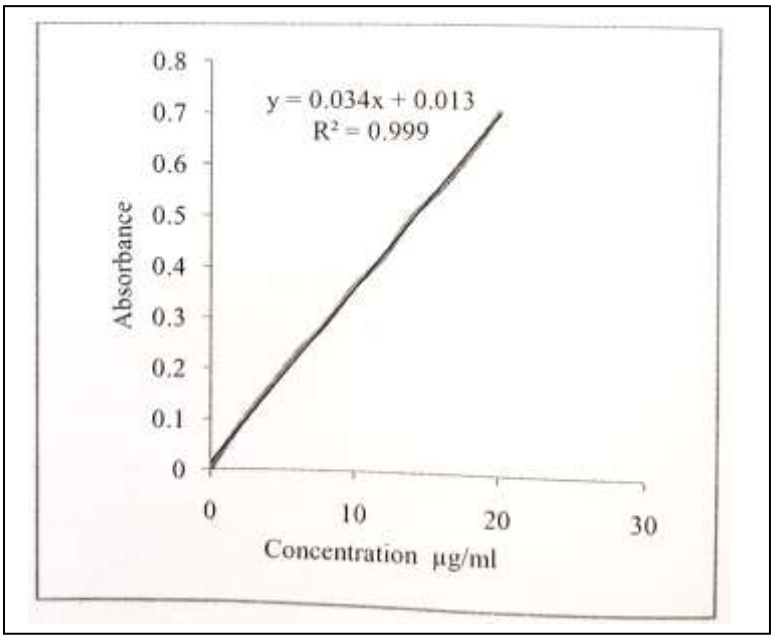
Calibration curve of DS was constructed in 0.1N HCl and phosphate buffer, pH 6.8. **Table 6.12** shows the absorbance of DS in 0.1N HCl solution containing 0-18 µg/ml of DS.and the absorbance of DS in pH 6.8 phosphate buffer solution was shown in Table 6.13.

Table 7.: Calibration curve of Diclofenac sodium in 0.1N HC1

Conc.(µg/ml)	Absorbance
0	0.000
2	0.015
4	0.025
6	0.034
8	0.045
10	0.056
12	0.066
14	0.077
16	0.087
18	0.096



Conc.(µg/ml)	Absorbance
2	0.085
4	0.157
6	0.228
8	0.288
10	0.36
12	0.42
14	0.498
16	0.554
18	0.624
20	0.701



5. UV Method Validation of Diclofenac Sodium

The system obeys Beer-Lambert's law in the range 2-20 µg/ml. Precision as well as other parameters like LOD, LOQ, and accuracy were also studied and the values are reported in the Table 6.17. All the parameters were studied and found within limits

Table 8.: Intraday precision

Conc. (ug/ml)	**Absorbance**			**Mean**	**SD**	**RSD**
	Trial 1	**Trial 2**	**Trial 3**			
8	0.298	0.288	0.280	0.288	0.0073	0.025
12	0.440	0.428	0.414	0.427	0.010	0.0248
18	0.624	0.622	0.645	0.630	0.0104	0.016

Table9. : Intraday precision (Day one)

Conc. (ug/ml)	**Absorbance**			**Mean**	**SD**	**RSD**
	Trial 1	**Trial 2**	**Trial 3**			
8	0.298	0.295	0.290	0.294	0.003	1.21
12	0.440	0.438	0.435	0.437	0.002	0.0046
18	0.624	0.628	0.620	0.624	0.0032	0.0052
8	0.278	0.288	0.283	0.83	0.0040	0.0144
12	0.420	0.437	0.441	0.432	0.009	0.21
18	0.617	0.635	0.610	0.620	0.010	0.016

Day two

Conc. (ug/ml)	**Day three**			**Mean**	**SD**	**RSD**
	Absorbance					
	Trial 1	**Trial 2**	**Trial 3**			
8	0.285	0.289	0.280	0.284	0.0036	0.0129
12	0.426	0.435	0.437	0.32	0.0047	0.011
18	0.620	0.617	0.622	0.619	0.002	0.003

Table 9.: Accuracy study for Diclofenac sodium

Level of Addition (%)	Tablet amount (mg)	Amount added (mg)	Drug found	% Recovery	Mean % Recovery
80	50	30	78.85	98.56	98.65
100	50	50	99.75	99.75	
120	50	70	117.18	97.65	

Table 10: UV Method validation of Diclofenac sodium

Parameter	Standard value	Observed value	Comment
Intraday precision	RSD <2.0	0.02193	complied
Intraday precision	RSD<4.0	0.14423	complied
Range	-	2-20 µg/ml	-
Limit of detection (LOD)	-	2.19 µg/ml	-
Limit of quantitation (LOQ)	-	6.636 µg/ml	-
Accuracy study	-	98.65%	-

Modifications Product of Okra polysaccharides:-

Physical Modifications: (Microwave Technique)

Modified product was analyses for any change in functional group, formulation was developed, % drug release was compared. IR of modified product in **Figure 6.6**

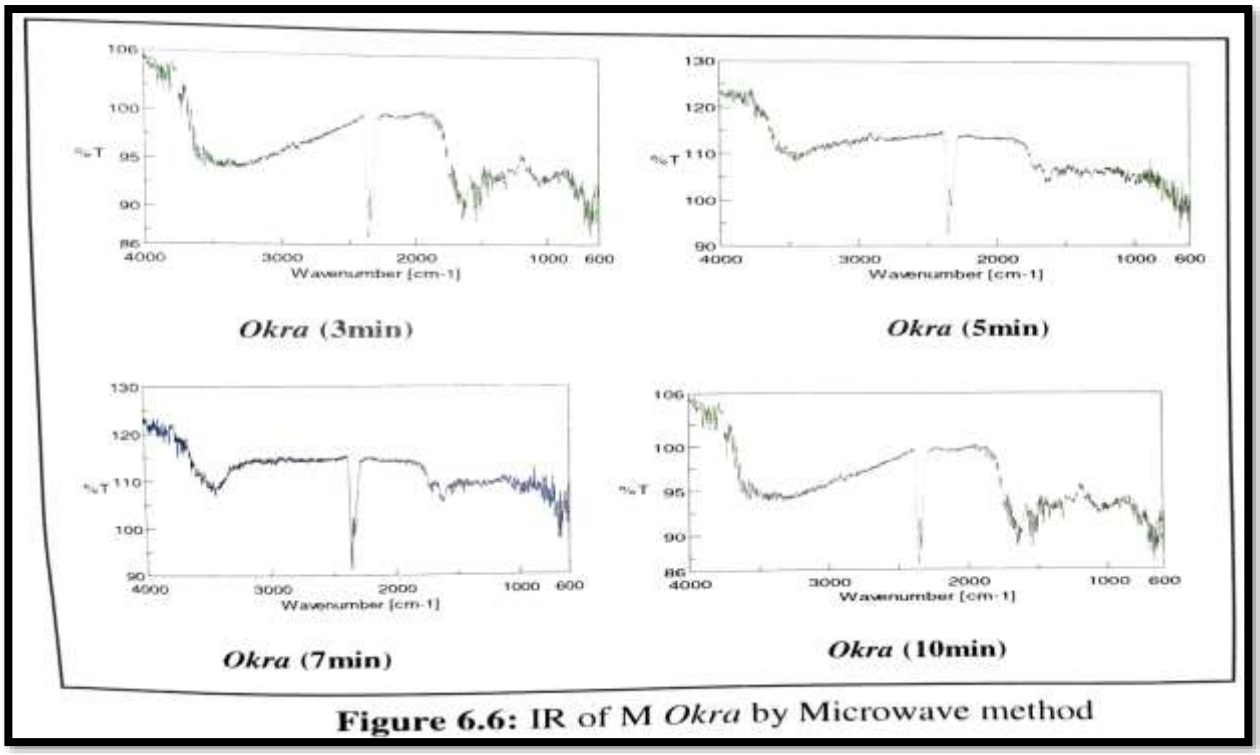


Figure 6.6: IR of M *Okra* by Microwave method

IR of M Okra did not show any change in chemical structure, modification or degradation up to 10 min.

2 Chemical Modifications:

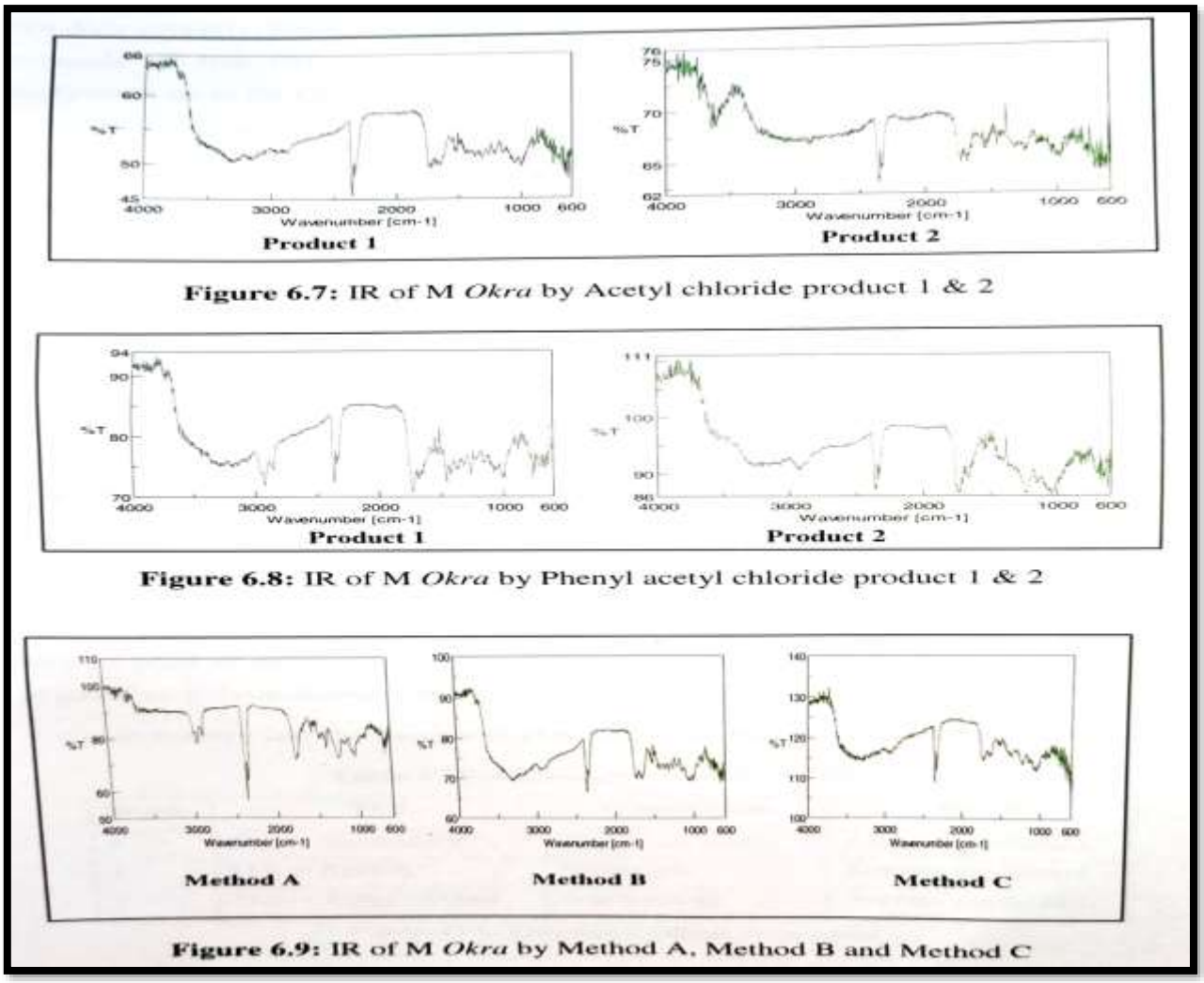


Figure 6.7: IR of M *Okra* by Acetyl chloride product 1 & 2

Figure 6.8: IR of M *Okra* by Phenyl acetyl chloride product 1 & 2

Figure 6.9: IR of M *Okra* by Method A, Method B and Method C

IR observed in M Okra by acetyl chloride, phenyl acetyl chloride and method B and C all of the product shown presences of free OH group, as broad peak of OH were observed from3000-3600 cm. so, it was concluded that the acetylation of Okra was not done properly. Modification of Okra polysaccharide by Method A doesn't show the presence of free OH group from 3200-3600cm hence there may be chances of acetylation on to the Okra polysaccharide. IR show Sharp peak at 1748.50 cm' for aryl ester i.e. for acetate. Sharp peak of C-H bending was observed at 719.31 which indicate aromatic compound.

CONCLUSION

In the present study, various approaches were tried for modification of Okra polysaccharide as sustained release matrix former. All the project study reveals following conclusions Okra polysaccharide was found to be matrix former in high Concentrations.Okra modification was done successfully by physical as well as chemical modification methods. Among these chemical modifications was found to be best possible method for formulation of SR matrix former. Drug-polymer compatibility study by IR Spectroscopy, which proves that there were no any chemical interactions. The order of increasing release retarding effect observed with various polymer as follows; M.Okra HPMC KISM> Pure Okra HPMC K4M> HPMC K100. Modified Okra was effective in very less amount i.e. 1/10th that of pure Okra used in SR formulation. Batch F5 was optimized batch of pure okra, while MAO4 was optimized batches of modified Okra by chemical method. In comparison with marketed formulations (Voveran and Vovo) Formulation batch MOA4 gives the close drug release with that of Vovo.F5 and MOA4 Formulation follows peppas model for sustained release in pH 6.8 PBS, while F5 showed zero order release mechanism in 0.IN HCl for 2hr and followed by pH6.8 PBS. Accelerate stability study also proves that formulation was stable for 60 days. The chemical modification of Okra polysaccharide of

vegetable origin, offer new polymeric materials with properties that can be exploited industrially.

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