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A Peer Review Of Xanthan Gum Derivatives In Development Of Drug Delivery Systems

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ABSTRACT: -

Xanthan gum is a microbial high molecular weight exo-polysaccharide produced by Xanthomonas bacteria (a Gram-negative bacteria genus that exhibits several different species) and it has widely been used as an additive in various industrial and biomedical applications such as food and food packaging, cosmetics, water-based paints, toiletries, petroleum, oil-recovery, construction and building materials, drug delivery. In Novel Drug Delivery System drug is targeted to the specific site of action to avoid 1st pass metabolism. For these types of dosage system conventional dosage forms are modified and designed to get approximately 100% of drug effect. Thus tablets, patches, hydrogels, microcapsules etc. forms of dosage are preparing in now days. To prepare this type of dosage forms controlled and sustained release polymers are added to provide precise amount of drug in time. Xanthan gum is one of the most useful natural polymers which is used to prepare dosage forms. To improve the efficiency and extended release pattern of the drug xanthan gum is modifying by processing chemical reactions such as carboxylation, acetylation, methylation, maleate reaction etc. these reactions helps to produce xanthan gum derivatives which is using in different types of hydrogels, tablets, patches etc. Xanthan gum is a high molecular weight extracellular polysaccharide. It is hydrophilic polymer, which until recently had been limited for use in thickening, suspending and emulsifying water-based systems. Xanthan gum derivatives are commonly used with other base materials like chitosan, acrylamide, poly vinyl alcohol, sodium alginate to make the formulation more stable. To evaluate the stability and therapeutically effect and the release order different type of analysis methods are used such as DSC, TGA, Swelling index, Release profile, Morphological examination, X-ray diffraction, TEM, SEM etc.

Keywords: - Xanthan gum, carboxymethylation, decarboxylation, acetylation, tramadol, microencapsulation, tablets.

1. INTRODUCTION

1.1 XANTHAN GUM: -

Xanthan gum is an important biopolymer discovered in the 1950s at the National Research Laboratories (NRRL) of United States Department of Agriculture (1). Xanthan gum is the natural polymer of a high molecular weight exopolysaccharide with branched chains and acidic characteristic produced predominantly by the plant bacterium (2) Xanthomonas campestris, it develops in aerobic conditions from sugar cane, corn or their derivatives. It is largely used as thickener agent in food & cosmetics (3). It has a main cellulosic chain with trisaccharide side chains composed of a mannosyl-glucuronyl-mannose attached to the C-3 position on an alternate glucosyl group(4). The thermal stability of Xanthan Gum against hydrolysis is far better than many other water-soluble polysaccharides or polymers. This because of the ordered helical structure of XG which protects the molecules from de-polymerization(5). So, viscosity of XG solutions is only affected

minimally by heat treatment steps for example sterilization proceeded. Xanthan Gum is also stable over a wide range of pH values. XG is known as fully biodegradable (completely within 2 days) naturally occurring polymer. However, due to the backbone similarity with cellulose, XG is resistant to the attack of the common cellulases and the tri-saccharide side chains of XG are likely to be a barrier to enzymatic attack. Only in disordered form, it can be catalyzed the cleavage of the main chain when attacked with fungal cellulases, not in ordered helical form (6). The molecular weight distribution of XG ranges from 2x106 to 20x106Da, depending on the association of chains forming aggregation of several individual chains and the variation in fermentation conditions It is used in sustained-release matrix tablets and suspending agent for sustained-release suspensions (7). It is also used in ophthalmic liquid dosage form because of xanthan gum delays the release of active substances, it helps to increase the therapeutic activity of pharmaceutical dosage forms and increases the retention time of dosages which is applied to the precorneal area (8). It can also be used in vaginal or topical formulations, due to its bio-adhesive strength increasing property. It is an excipient for spray-drying and freeze-drying processes. Xanthan gum is a water-soluble polysaccharide but it has the disadvantage of a slow rate of dissolution, particularly at high concentrations & in cold water (9). To overcome these problems, chemical modification of this natural polymer is necessary to improve its solubility and to develop novel functions that allows for a wider range of applications. It is generally prepared by natural microbial fermentation process which converts glucose to produce this product of economic importance (10). Various modification methods have been done on XG to solve its limitations such as; microbial contamination, reduce its thermal stability throughout processing and storage XG. Carboxymethylation is a well-known etherification process for polysaccharides, in which hydroxyl group are etherified with carboxymethyl groups (11). Carboxymethyl xanthan gum can be used for controlled drug delivery of bovine serum albumin, for prolonged release of diltiazem, and protein delivery. The rheological properties of xanthan gum and its uniqueness compared to other gum render it to be used in other industries such as oil, paper, agriculture, textile, cosmetic industries etc. (12)

1.2 PROPERTIES OF XANTHAN GUM

1.2.1 Molecular structure of xanthan gum: -

Xanthan is composed of penta-saccharide repeating units, containing d-glucose, d-mannose, d-glucuronic acid (at a ratio 2:2:1), acetal-linked pyruvic acid and d-acetal groups (13). The primary structure of xanthan gum is a linear (1→4) linked to the β-D-glucose backbone with trisaccharide side chain on all other glucose at C-3, containing a glucuronic acid residue linked (1→4) to a terminal mannose unit and (1→2) to a second mannose that connects to the backbone(14). The terminal mannose can be attached with a pyruvate group & the mannose adjacent to the main chain could have an acetyl group attached to C6.

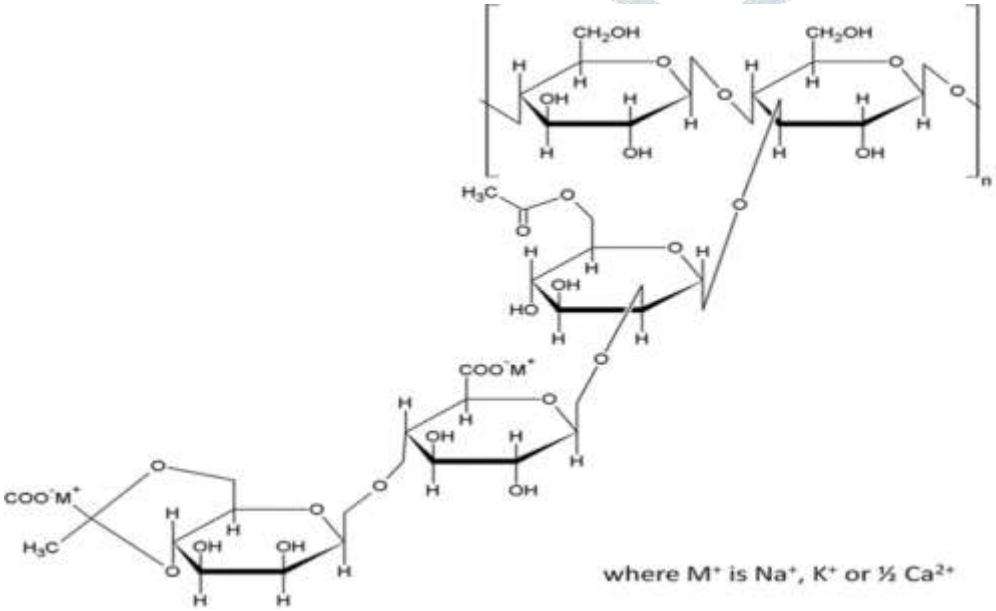

Fig 1.2 : - structure of xanthan gum

Molar mass: - 933.748 g. mol^{-1}

Chemical formula: - $C_{35}H_{49}O_{29}$ (monomer)

Solubility: - soluble in water

Density: - 1500 kg/m^3

Melting point: - 274^0C

1.2.2 Physical properties of xanthan gum: -

1. Xanthan gum soluble in both cold and hot water and in general, it is not affected by changes in pH value.(15) Xanthan gum will dissolve in most acids or bases. Xanthan gum with all hydrocolloids bind water.
2. The viscosity of xanthan gum is stable at low pH values and at high temperatures for a long period of time is not affected by addition of large amount of salt (16).
3. It has water binding capacity, so xanthan gum solutions exhibit good freeze stability (17).

1.3 USES OF XANTHAN GUM: -

1. Xanthan gum is used in pharmaceutical industries as emulsifying and suspending agent. They effectively stabilize the emulsion via interfacial absorption (18).
2. Xanthan gum is used as polymer for sustaining material in dosage form. It has used in tablets, suspension as or as matrix system for controlled drug release(19).
3. It is also used as coating agent which sustain the release and as gelling agent for NDDS formulations (20).

1.4 XANTHAN GUM IN DRUG DELLIVERY SYSTEM

• A Controlled release of drug delivery is essential in order to increase the effectiveness of drug therapy.
• This also reduce the chance of toxic condition caused by rapid drug level in the plasma and can also avoid repeated administered of drug.
• Targeted drug delivery system is highly recommended for colon associated diseases namely colitis ulcers, Crohn syndrome, amebiasis, colorectal adenocarcinoma, general delivery of protein and peptide drugs (21).
• Oral route of administration is the most preferred one but the probability of drug release of active ingredient, a controlled release is to be achieved which can be obtained using some controlled release mechanisms (22).
• Xanthan gum is selectively degraded in the colon not in stomach and small intestine.

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1.5 Modification in xanthan gum and its effects: -

1.Modification with formaldehyde

- It decreases the intermolecular interactions, It possess swelling and dissolution.

2. Grafting with acrylamide

- Swelling decreased and faster release of drug.

3.Carboxymethylation

- Lowered Viscosity & faster release of drug.

4. Grafting with ethyl acrylate

- Improves the metal uptake property and more thermo stable.

5. Grafting with 2-acrylamidoglycolic acid

- Improved thermo stable and resistant from biodegradation, Better swelling, metal ion absorption property.

6. Chemo-enzymatic amylase grafting

- Double helix conformation.

7. Grafting with 2-acrylamido-2-methyl-1-propane sulphonyl acid

- Increases the elasticity of hydrogel, Enhancement in water swelling capacity, metal uptake & its retention.

8. Plasma enhanced modification with di-chlorosilane

- Enhances the network strength and stability in gelling.

1.6 XANTHAN GUM AND ITS DERIVATIVES IN POSSIBLE FORMULATION/DOSAGE FORM

S.N.	ative	Dosage Form	Drug Used	Release Profile
1.	Xanthan gum	Matrix tablets	Caffeine, Indomethacin, Sodium Indomethacin,	The swelling of XG matrix tablets shows a reciprocal relation of In-vitro release with concentration of salt. Drug release was affected by ionic strength and concentration of buffer. Drug release depends on swelling behavior
2.	Xanthan gum and Hydroxy-propyl methyl cellulose /& guar gum	Matrix tablets	Caffeine, Indomethacin, Sodium Indomethacin, propranolol hydrochloride	Comparative investigation to assess the performance (23). A quite similarity was found in Compaction behavior. XG is more readily flowable than HPMC. Drug release profile were explained by hydrophilicity (24).
3.	Xanthan gum and xanthan gum-n-octenyl succinate starch	Matrix tablets	Ibuprofen	The xanthan gum/CL490 matrix tablets of a 1:4 and a 1:10 ratio both released nearly 100% after 24 h. The combination of a xanthan

				gum and CL490 showed that it avoids the initial slow absorption phase in vivo that occurred with a pure xanthan gum matrix tablet (25).
4.	Xanthan gum and Hydroxy-propyl-methyl cellulose	Matrix tablets	Caffeine, Indomethacin, Sodium Indomethacin	Diffusion through the hydrated mass is not affective factor for release of an insoluble drug like indomethacin from XG matrix tablet.
5.	Xanthan Gum: Guar Gum (10:20)	Matrix tablets	5-FU	In-vitro drug release was found to be 42.6% to 67.2% with 2% and 80.34% with 4% rat caecal medium.
6.	Xanthan gum and Galactomannan	Compressed tablets	Theophylline	The XG/SD showed that 8% of the tablets were having the release rate about 90% at the end of 8 h, with zero-order release kinetics(26). Tablets containing galactomannan (VO) in low concentration showed a complete erosion, while the others had fast hydration and swelling in contact with the dissolution medium (27).
7.	Xanthan gum and Ethyl cellulose	Mini-matrices	Ibuprofen	Increasing xanthan gum concentrations yielded a faster drug release due to a higher liquid uptake, swelling and erosion rate.
8.	Xanthan gum and Chitosan	Tablets	Chlorpheniramine maleate	In 0.1N HCl, the HME tablets formed a hydrogel that functioned to retard drug release in subsequent pH 6.8 and 7.4 phosphate buffers. Tablets without chitosan did not form a hydrogel to retard drug release in 0.1N HCl (28).
9.	Acrylamide grafted xanthan gum	Tablets	Atenolol, Carvedilol	- pAAm-g-XG matrix tablets containing ATL, the release continued up to 24 h by releasing 85% of the drug in SGF and SIF media. Release time increased with increasing grafting ratio of the grafted copolymer.

10	Xanthan gum and sodium alginate	Beads	Diclofenac sodium	0.3%XG–DCA beads could retard the drug release in distilled water because interaction between XG and SA gave higher tortuosity of the bead matrix. XG could modulate physicochemical properties and drug release of the DCA beads.
11	Xanthan gum: Boswellia gum (3:1) with 300mg total coat weight and Boswellia gum: HPMC (2:3) with 275mg total coat weight	Compressed coated tablets	5-FU	- In-vitro drug release was found to be 80.2% which was increased upto 98.22% with 2% rat caecal medium
12	Xanthan gum with Konjac glucomannan, KGM (20%TWG)	Matrix tablets	- Cimetidine	XG shows more In-vitro drug release than konjac-glucomannan. Mannose accelerates drug release from matrix tablets prepared by Konjac-glucomannan but no effect on tablets prepared by XG (29). Matrix tablets with a single polysaccharide (either XG or KGM) could not retard drug release from tablets effectively while XG: KGM complex does.
13	Konjac glucomannan and Konjac glucomannan/ xanthan gum	Gel	Theophylline anhydrous, Diltiazem hydrochloride	Drug diffusion experiments demonstrated that XG proportion and its synergistic interaction with KGM was the main responsible for the control of diffusion in the binary systems (30). Gels based on XG and the Japanese or the European KGM were found useful to develop theophylline or diltiazem delivery systems capable to maintain physical integrity and to control the release for 8 h.
14	Xanthan gum with Konjac glucomannan (both American and Japanese varieties)	Matrix tablets	Diltiazem Tablets	- In vitro drug release with Japanese KGM drug release was complete within 24 h in the presence of mannose. There was a smaller effect on release from formulation of American KGM.

15	Carboxymethyl xanthan gum and resin	Beads	- Diltiazem	75–82% drug was released in 2 h in SGF from various beads, 75 to 98% drug was released in 5 hours in SIF indicating the dependence of drug release on pH of dissolution media.
16	Xanthan gum	suspension	Fe and Fe3O4	- Xanthan gum gels 6 g/ml were possible to avoid the sedimentation of 30 g/L of RNIP-10 iron nanoparticles for period of 10 days (31).
17	Sodium carboxymethyl xanthan gum	Microparticles	Bovine serum	The microparticles coated with 0.5% aqueous solution of either SCMX gum or sodium alginate did not liberate a substantial amount of entrapped protein within the same period and prolonged the release in PBS solution (pH 7.4) up to 10 and 12 h, respectively(32).
18	Xanthan gum and Xanthan-g-poly (acrylamide)	Tablets	Diclofenac sodium	Drug released by zero-order kinetics, and the faster release of drug was observed from the graft copolymer matrix as compared to the xanthan gum matrix. Grafting reduces the swelling, but increases the erosion of xanthan gum (33).
19	Xanthan gum-sodium alginate	Transdermal Films	Domperidone	The films were prepared using xanthan gum (XG) and sodium alginate (SA) by varying the blends compositions viz., 10:0, 8:2, 6:4, 5:5, 4:6, 2:8, and 0:10 (XG/SA, wt /wt, %). Transdermal films can be used to achieve controlled release of drug and improved bioavailability .
20	Sodium carboxymethyl xanthan gum and sodium alginate	Beads	Ibuprofen	Increase in the concentration of cross-linking agent tended to increase the drug release. The 14% of the loaded drug was released in 2 h. Complete drug release was achieved in PB solution

				within 210 to 330 min depending upon the formulation variables.
21	Sodium carboxymethyl xanthan gum	Beads	Diltiazem	40% and 80% drug was released in 2 hours in pH 1.2 and in 5 to 6 h in pH 6.8 respectively from polyethyleneimine treated xanthan beads. The prolonged release was attributed to decreased swelling of the beads due to PEI treatment.
22	Sodium carboxymethyl cellulose and xanthan gum, gum karaya and locust bean gum	Tablets	Metoprolol tartrate	Formulation containing combination of xanthan gum and locust bean gum in ratio 2:1 exhibited complete drug release in 45 mins but poor drug permeation.
23	Xanthan gum and poly vinyl alcohol	Microspheres	Diclofenac sodium	Xanthan gum (XG) and poly vinyl alcohol (PVA) was used to develop pH-sensitive interpenetrating network (IPN) microspheres by emulsion cross-linking methods. Microparticles show slow and prolonged drug release when compared with DS solution (34).
24	Xanthan gum	Floating tablets	Diltiazem	Low amount of xanthan gum (40%w/w) showed low release rate as compared to formulation containing higher concentration (60% w/w).
25	Starch, Xanthan gum and sodium tri-metaphosphate	Films	Ibuprofen sodium, Sodium salicylate, Vitamin B12, Pyrogallol Red, Methylene Blue (35)	The hydrogel exhibited selective permeability depending on drug charges. The selective permeability can be potentially useful for the design of controlled release formulations of ionizable drugs (36).
26	HPMC-Xanthan gum and Eudragit	Floating microsphere	Ranitidine hydrochloride	Floating microspheres of Ranitidine Hydrochloride with HPMC K 100, Xanthan gum and Eudragit S 100 and in various ratios of 1: 1, 1: 2, and 1: 3. Floating microspheres were prepared to achieve an extended

2.					retention in the upper gastrointestinal tract, which may result in enhanced absorption and thereby improved bioavailability (37).
	27	Xanthan gum and chitosan blend	Hydrogel	Luciferase enzyme	Enzymatic activities of the encapsulated enzyme were confirmed over 30 days.

METHODS FOR FORMULATIONS OF NOVEL DRUG DELIVERY SYSTEM

2.1 Microencapsulation Of Blueberry Anthocyanins By Combination Of Carboxymethyl Starch And Xanthan Gum

Materials

Carboxymethyl starch (CMS), XG (xanthan gum), Blueberry anthocyanin (cyanidin-3-Oglucoside and peonidin-3-glucoside as two main anthocyanin).

Method

The suspension of CMS/XG in the concentration of 30/1, 60/1, 90/1, 120/1, 150/1, w/w were prepared in distilled water at room temperature (25 ± 1° C) and then kept in refrigerator for 24 h to compete hydration for the wall material. The solution was prepared with the addition of a previously weighed quantity of blueberry anthocyanins to the wall material suspension (39). The blueberry anthocyanins and wall materials were mixed in a weight ratio of 1:4 (anthocyanins: wall material) (40). The solid content was maintained at 10% w/w. A blank without XG was prepared as the control solution to analyze. The mixture was prepared for 4 min in a high shear mixer. The mixture of anthocyanins and CMS/XG or CMS was poured into a flask and kept in a freezer at −78° C, and dried in a freeze dried at −58° C under pressure for 42 h. Thereafter, the dried product was ground by a pestle- mortar, and then stored in brown glass bottles in a freezer (−18° C) until the analysis is completed. The blueberry anthocyanins-loaded microcapsules prepared from different wall materials were named CMS/XG (30/1)-ANS, CMS/XG (60/1)-ANS, CMS/XG (90/1)-ANS, CMS/XG (120/1)-ANS, and CMS/XG (150/1)-ANS. A blank was prepared as the control, named CMS-ANS (40).

(3,12,13)

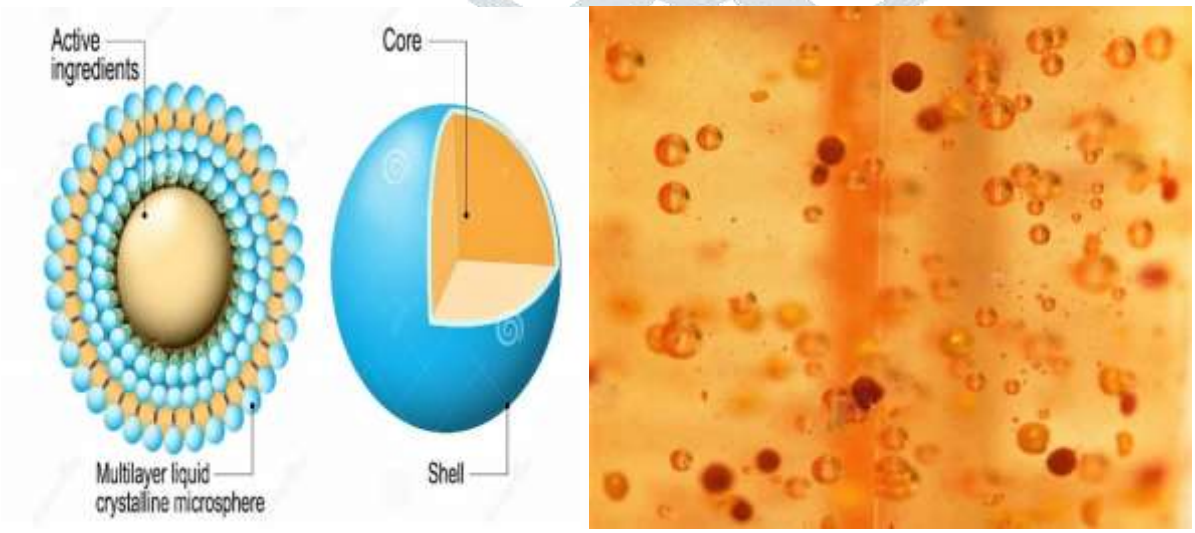

Fig 2.1 structure of microcapsule and microspheres

2.2 Spray-Dried Microcapsules Of OSA-Modified Starch And Xanthan Gum For Controlled Release Of CLA

Materials

OSA-modified corn starch, XG (average molecular weight: 366 ×104g/mol), CLA (a mixture of cis-9, trans-11 and cis-10, trans-12 octadecadienoic acids, linoleic acid <1%). Chemically pure bile salts, n-hexane, and light petroleum, pancreatin.

Preparation of CLA-loaded microcapsules

Suspension of OSA/XG in the ratio of 60/1, 80/1 and 100/1, w/w were prepared for the wall material. It is then stirred stored for overnight at room temperature 25^0C. A pre-weighed quantity of CLA to the wall material suspension was added to prepare the emulsions. The mass ratio of the wall material to CLA were 4:1. The solid content of the emulsions was maintained at 10% w/w. A blank without XG was prepared as the control (41). The mixture was homogenized for 2 min with a rotational speed of 20,000 rpm in mixer and homogenized for five times with a high-pressure. Then CLA emulsion was fed into a spray dryer with a peristaltic pump and sprayed into the drying chamber at an inlet air temperature of 160 ± 5° C and outlet air temperature of 75 ±5° C and inlet-outlet air volume were controlled. (4)

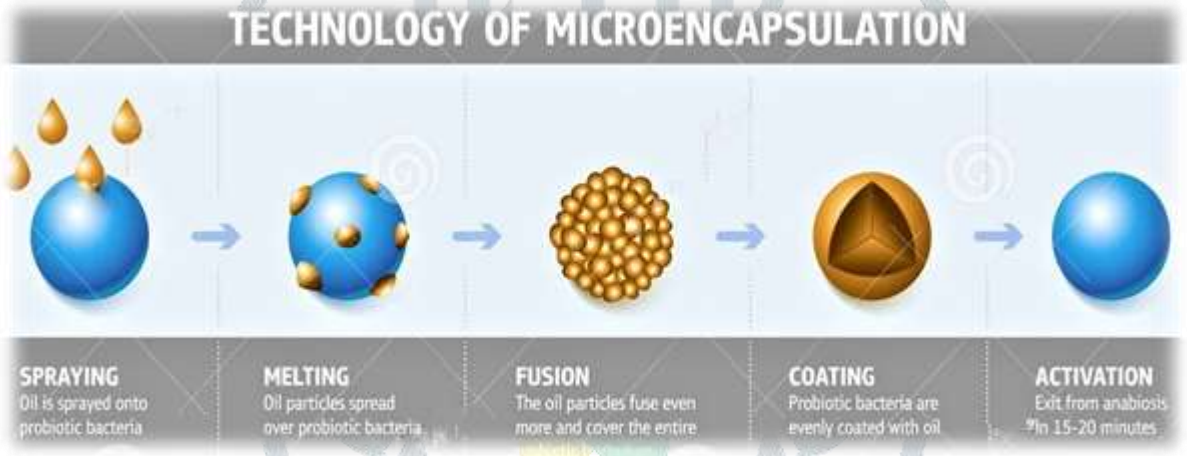

Fig no2.2. ***Technology of microencapsulation***

2.3 Encapsulation Within Modified Xanthan Gum- Chitosan Based Hydrogel

Materials

Xanthan gum, Chitosan with degree of deacetylation 95%, monochloroacetic acid, dimethyl sulfate, sodium hydroxide, HCl, sodium chloride, ethanol and other solvents used ciprofloxacin.

Synthesis of polysaccharide-based materials

1. Synthesis of N-trimethyl chitosan (TMC)

Preparation of TMC is done by the methylation reaction of chitosan and dimethyl sulfate. Chitosan 3g was added to 50 ml of dimethyl sulfate and 10 ml of distilled water, and then 3.6 g of NaOH and 2.5 g of NaCl were added (42,43). The mixture was refluxed for 6 hours at 70° C & continuous stirring. Then prepared solution was dialyzed against distilled water for 3 days. Acetone was added to precipitate the product then filtered, washed for several times with ethanol and dried in vacuum oven at 80° C for 24 h.

2. Synthesis of carboxymethyl xanthan gum (CMXG)

Carboxymethyl of xanthan gum was prepared previously. XG powder 5g was suspended in 100 ml of ethanol and stirred it for 30 min at room temperature. Then, 5 ml of NaOH solution was added to the solution gradually

under continuous magnetic stirring. After that 4g of monochloroacetic acid dissolved in 10 ml of distilled water was then added dropwise to a period of 30 min. The mixture was heated to a temperature of 50° C (44). The pH was adjusted of the suspension to neutrality with HCl/ethanol mixture (20/80). At last isolated product was washed with ethanol and then dried in vacuum at 80° C for 24 hours.

3. Synthesis of (TMC/CMXG) hydrogel

Dissolve the 0.5 g of CMXG in 50 ml of distilled water under vigorous stirring for 3 hours. Then 0.5 g of TMC was dissolved in 50 ml of distilled water dropwise. This mixture was then kept under constant stirring for 2 hours at room temperature (45,46). The hydrogel was prepared which is collected by centrifuge. After that washed the hydrogel for several times with distilled water & left to dry at 25°C.

Chemical reaction: -

$$Cs{-}N(CH_3)_3^+ \quad + \quad {}^-OOC{-}CMXG \xrightarrow{yields} Cs{-}N(CH_3)_3^+ \; {}^-OOC{-}CMXG$$

TMC CMXG PEC of TMC/ CMXG hydrogel

Fig 2.3 i): - synthesis of TMC/CMXG hydrogel

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Fig2.3 ii) Hydrogel

Drugs loading in the prepared hydrogel

In order to investigate ciprofloxacin loading in hydrogel, 0.1 g of hydrogel was added to 50 mL of freshly prepared drug solution at 37 °C and 100 rpm. After 24 h. of incubation at shaking incubator, the solution was filtered and an aliquot of the supernatant was analyzed at 276 nm in a UV–Visible spectrophotometer (UV–VIS-NIR Scanning spectrophotometer).

$$\% \text{ of drug loading (DL)} = \times \frac{\text{amount of drug in gel}}{\text{amount of gel}} \times 100$$

2.4 Deacetylated Xanthan Derivatives in Chitosan-Based Polyelectrolytes for The Sustained Release of Tramadol Tablets

Materials

Xanthan gum with a molecular weight of 2.5 $\times 10^6$ g/mol and 39% of acetylated group, chitosan with mw of 190,000 g mol and 83.4% deacetylated, tramadol hydrochloride, magnesium stearate and lactose monohydrate. The other useful reagents are HCl, KOH, phosphoric acid, NaOH, sulfuric acid and ethanolic alcohol.

Method

The deacetylation reaction consisted of an alkaline hydrolyze of XG using sodium hydroxide aqueous solutions at different concentrations 0.0025, 0.005, 0.0075 and 0.01 mol/L. The deacetylation was performed with 1% XG aqueous solutions where, 125 ml of each solution were filled in Erlenmeyer flasks and placed on a magnetic agitator at a speed of 300 rpm. These reactions were carried out at a room temperature for duration of 3 hours. Then obtained product was neutralized with 2M HCl solution. The modified polysaccharides

precipitates which was recovered with ethanol in the proportion of 1:4 (v/v), then it was dried at 56° C until a constant weight and then pulverized to get a fine particle size, for sieving analysis, sample was placed on the sieve (200, 150 mm) in mechanical shaker (47, 48). The sieving analysis is considered as complete when the weight of any of the test sieves. The mass fraction on the 150 mm sieve was used in the characterization and formulation tests.

Reaction of deacetylation: -

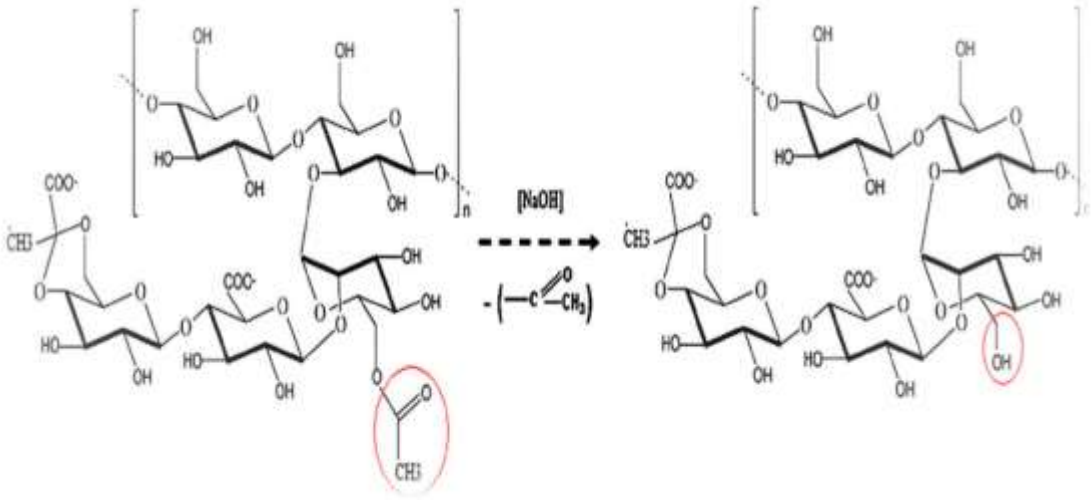


Fig 2.4.i) deacetylation reaction of xanthan gum (6)

Fig 2.4 ii) *Tramadol tablet*

2.5 Formulation Of Xanthan Gum-Based Bilayered Mucoadhesive Buccal Patches Of Zolmitriptan

Materials

Hydroxy propyl methyl cellulose, zolmitriptan, Xanthan gum, propylene glycol, polyvinyl alcohol, sorbitol and dimethyl sulfoxide, triethylamine and ammonium dihydrogen orthophosphate, acetonitrile, oleic acid.

Preparation of mucoadhesive bi-layered buccal patches

Zolmitriptan mucoadhesive bi-layered buccal patches is prepared by solvent casting method. ZMT was dissolved in distilled water. Then XG was added to the solution, heating applied till the gum dissolved. The hydrophilic polymer PVA was then added to this solution. Kept it for 20 min for swelling of the polymer. After then HPMC was added and this solution was kept in refrigerator for the purpose of cooling till a clear solution was obtained (required 30 min). After sometime PG was added as a plasticizer and stirred with constant mechanical stirrer for 10–15 min(49,50). This solution was then sonicated for 30 min for complete removal of air bubbles. The resultant clear solution was then poured and placed in glass Petri plate of size 7 cm in diameter and allowed to dry in a hot air oven, maintained at 50° C for 5 h. The dried bi-layered patch

was then cut into circular pieces having diameter of 2 cm and area as 3.14 cm^2, containing 2.5 mg of drug per patch. (7,15)

Fig.2.5 Bi-layered transdermal patches

2.6 Biodegradable-Stimuli Sensitive Xanthan Gum-Based Hydrogel and Controlled Drug Release

Materials

Xanthan gum, Acrylic acid, acrylamide, glutaraldehyde and urea, beef extract, NaCl and agar, bacterial strain. All the chemicals were of analytical grade and used without further purifications, distilled water.

Synthesis of Gx-cl-poly (AA)-MW

Xanthan gum 1.0g was suspended in 14 ml of distilled water and stirred it continuously till homogenous thick slurry was formed. Acrylic acid and glutaraldehyde dropwise added in the suspension with continuous stirring. The known amount of APS for free radical initiator was added by transferring the mixture to the microwave oven which is operating at 100% power (850 W) (51). The synthesized graft co-polymer was cooled at room temperature and washed thoroughly with distilled water to remove the formed traces of homopolymer and it was subsequently allowed dry in hot air oven at 65 °C till no detectable change in weight was observed.

Various process parameters such as reaction time, concentration of acrylic acid, APS and glutaraldehyde solvent amount and pH were optimized to get maximum percentage of swelling (Ps) which was calculated as per Eq. (1):

$P_s = w_s - w_d / w_s \times 100$

Where, w_s and w_d respectively the weights of swelled and dry sample, respectively.

The percentage grafting P_g was also calculated Eq. (2)

Scheme 1. Schematic representation for the synthesis of Gx-cl-poly(AA)

$P_g = w_f - - w_d / w_f \times 100$

where, w_f is the weight of the functionalized polymer and w_d is the weight of the polymer backbone.

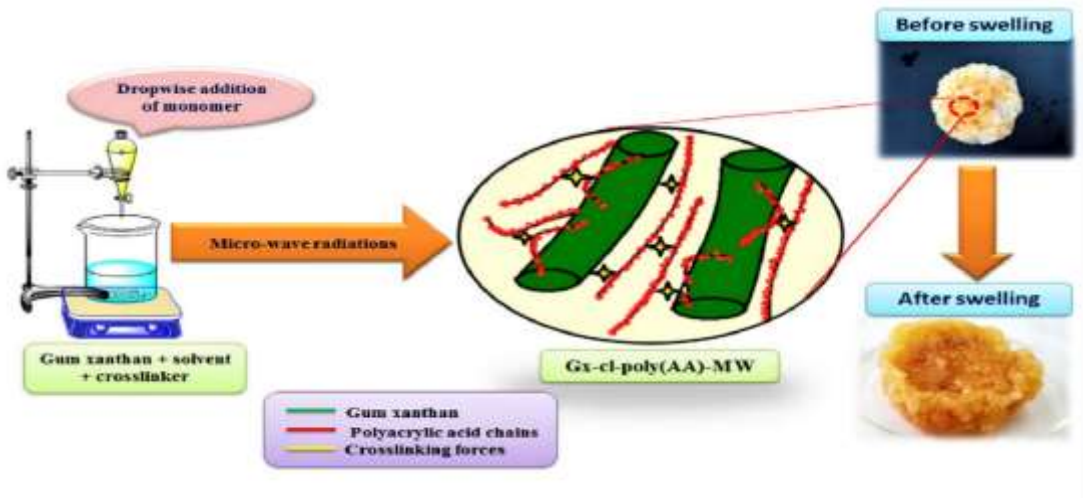


Fig 2.6: -. Schematic representation for the synthesis of Gx-cl-poly (AA)-MW. (8,9)

*3.*DISCUSSION

3.1 Discussion of CMS/XG-ANS microcapsules

3.1.1 Encapsulation efficiency –The comparison of efficiencies between only CMS microcapsules and CMS/XG shows that there is no significant difference in encapsulation efficiency of the microcapsules prepared by different proportions of carboxymethyl starch and xanthan gum combinations. Addition of xanthan gum in different amount to the original wall material had no significant effect on the encapsulation efficiency. According to some studies the encapsulation efficiency is related to the wall viscosity of microcapsules, but the excess of viscosity than the optimum viscosity could not affect the encapsulation efficiency, the improvement in efficiency is not significant.

3.1.2 Thermostability-The thermal stability of the product is analyzed by TGA in the temperature range of 30–300 °C for the evaluation of degradation. the thermal stability of Anthocyanin is affected by reaction of CMS and xanthan gum. In 100^{o}C temperature the sample losses its initial weight. In the second stage the rate of difference in weight loss is measurable. The maximum rate of weight loss occurred at 130.36 °C (approximately) for Anthocyanins, the maximum rate of weight of CMS/XG-ANS microcapsules approximately at 217.17^{o} C.

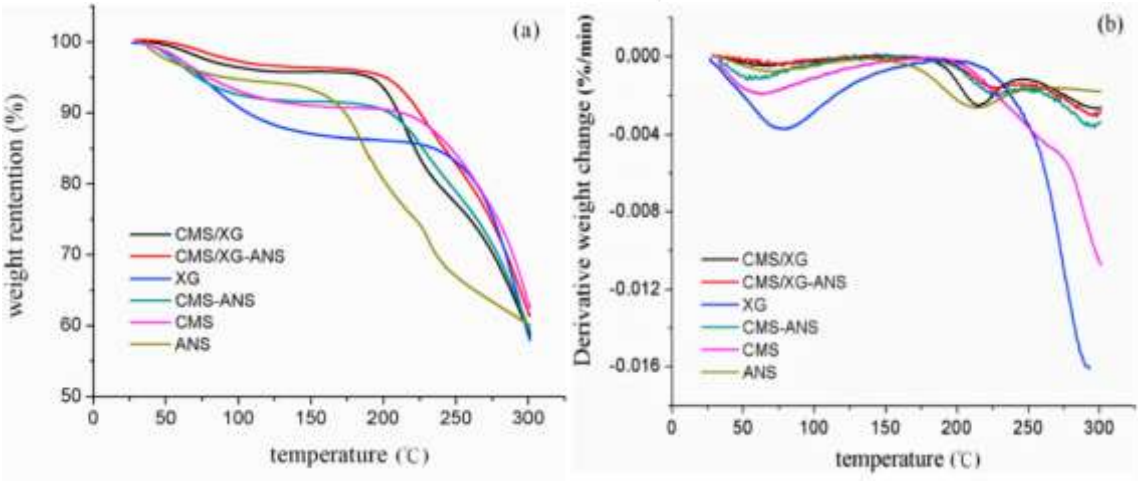


Fig 3.1.2. ***TGA (a) and derivative TGA (b) curves of CMS/XG(90/1)-ANS, CMS/ANS, CMS/XG,CMS, XG, ANS.***

3.1.3 Release profile: -

The release of anthocyanins decreased with the increase of XG amount in the system. The increase in release of anthocyanin from CMS/XG (60/1) microcapsules in gastric fluids is 21.24% in comparison of 35.68% from CMS-ANS microcapsules. The release of drug in the intestinal fluid is enhance upto 70%. The release is decreased with the increase in xanthan gum content. (18,19,20)

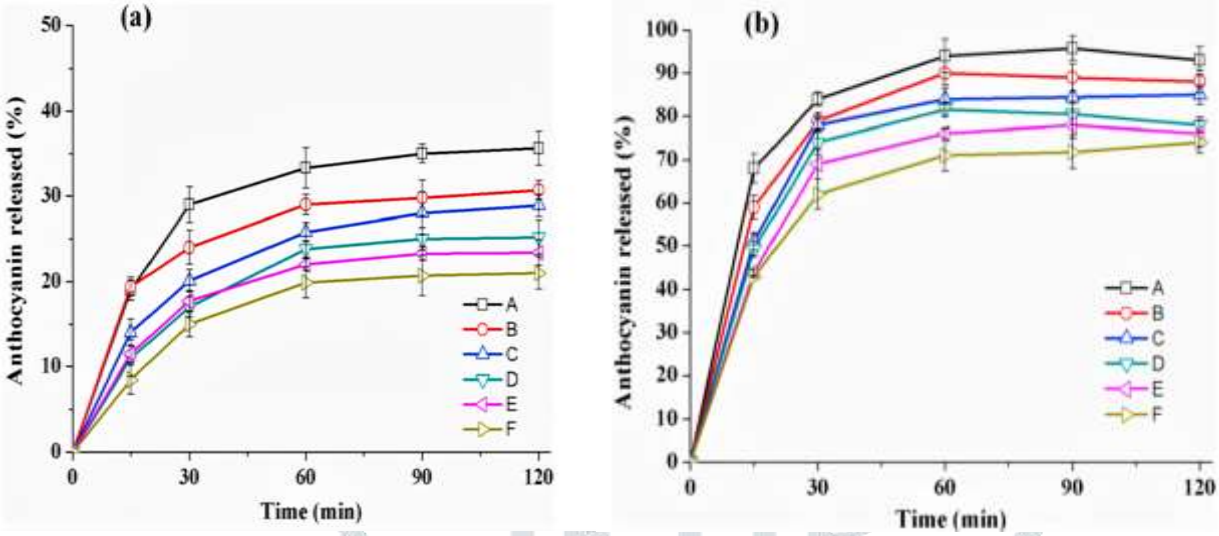


Fig 3.1.3: - in vitro release of anthocyanin from (A) CMS-ANS, (B) CMS/XG (150/1), (C) CMS/XG (120/1)-ANS, (E) CMS/XG (60/1)-ANS, (F) CMS/XG (30/1)-ANS under stimulated gastric (a) and intestinal (b) condition.

3.2 Discussion of CFX loaded TMC /CMXG hydrogel

3.2.1 Swelling property –

The swelling of polymeric matrix controlled the release of drug. The swelling property is necessary for the release of drug, swelling of matrix allows the release. In phosphate buffer solution of pH 7.4 at 37^0 C shows the gradually improvement in release with increasing the immersion time, reaches to maximum after about 240 min (52). The rate of penetration of buffer solution into the prepared hydrogel reduces the drug loading and the release time from the hydrogel. So, it can be used in drug delivery applications where intended to rapid release (53,54). The TMC/CMXG hydrogel is effective in gram positive bacteria, hydrogel releases the antibacterial drug into the bacterial cell after successful loading. The drug release happened due to the penetration of fluid or water into the hydrogel so the rate of drug release reduces gradually (55).

3.2.2 FT-IR Characteristic-

The FT-IR spectrum of TMC/CMXG hydrogel showed characteristic peaks of TMC and CMXG individually (Fig. 3.2.2-a). For hydrogel, the absorption peaks of -OH and -COOH molecules of CMXG are showing lower wavenumber in comparison with xanthan gum. -C=O of the -COO− showing the absorption peaks of the CMXG, which is shifted from 1635 to 1600 cm^{-1}. The molecular interactions between the -OH, -COO groups of CMXG and quaternary amino group of TMC causes the shifting of higher wavelength. The FT-IR spectrum of CFX drug (Fig. 3.2.2-b) plots the characteristic absorption bands at 1696 cm^{-1} of carbonyl group, 1480 cm^{-1}, 3490 cm $-^{1}$ due to O−H stretch, 3320 cm^{-1} due to N−H, C−O stretch of quinoline causes 1605 cm-1, N−C stretch causes 2840 $cm^{-1}$and aliphatic C−H stretch causes 2930 cm-1.

A comparison revealed that there was no effect on functional groups as the main characteristic peaks of the ciprofloxacin was found intact in the spectra, between FTIR spectra of ciprofloxacin and TMC/CMXG hydrogel covered ciprofloxacin(56). So that there was no significant interaction between CFX drug and the hydrogel.

(18, 20)

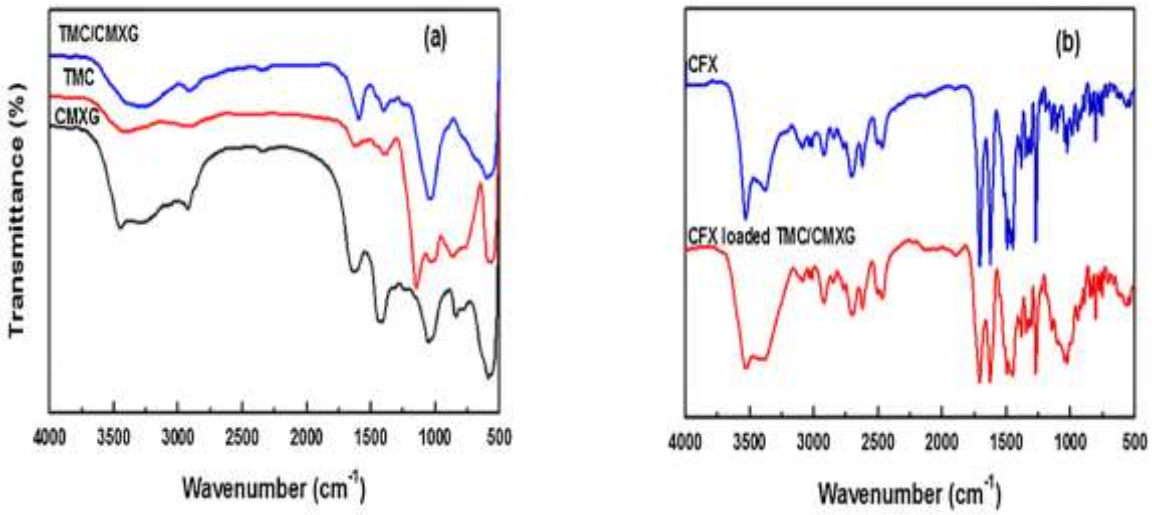


Fig.3.2.2-a ***FT-IR spectra of TMC, CMXG and TMC/CMXG hydrogel***
Fig. 3.2.2-b ***Neat CFX loaded TMC /CMXG hydrogel***

3.3 Discussion of OSA/XG microcapsules: -

3.3.1 Encapsulation efficiency-

The efficiencies of encapsulation are observed in OSA and OSA/XG microcapsules. All samples exceeded 97% of the efficiency which is sufficient for the formulation but the small amounts of xanthan gum do not show any significant changes in the encapsulation efficiencies compared to that observed in the control. There were no changes after adding extra amount of XG in efficiency for increase in the viscosity during drying. When the OSA/XG ratio increased to 60/1, then the encapsulation efficiency decreased (57). To get the improved efficiency and optimum retention then an optimal viscosity is required. The improved retention is owing to slow internal droplet circulation. However, increasing the viscosity over the optimism showing the barriers in droplet formation and reducing retention.

3.3.2 Thermal stability tests –

The determination of decomposition temperature and the mode of decomposition upon heating is important to the proper processing temperature (58). The TGA curves provides the data effect of heating on the microcapsules. The degradation in the xanthan gum in observed near at 100 °C due to water desorption. In the CLA and spray-dried materials there was a small amount of water adsorbed, the second weight loss in the XG occurred at 222.2 °C with total weight loss 48.6%.

The OSA microcapsules had a initial weight loss at 226.3^{o} C and OSA/XG microcapsules at 236.1°C, respectively. Weight loss in CLA causes upto 86.7% at 156.0 °C, where the OSA/XG-CLA microcapsules showed an 88.9% weight loss at 243.5 °C, the capsules were thermally stable from 100 to 160°C. this range is optimum for improved production.

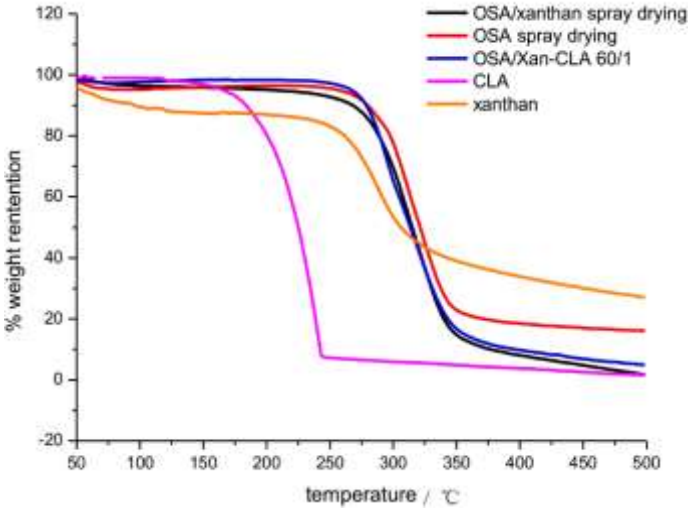


Fig. 3.3.2 The thermogravimetric curve of CLA, xanthan, OSA spray drying, OSA/xanthan spray drying and OSA/xanthan-CLA microcapsules

3.3.3 Surface characterization –

the morphological characteristics of the powders of CLA microcapsules prepared from different ratios of wall material. The most of the microcapsules showed a surface morphology lacking of cracks, the wall materials demonstrating the strong viscoelastic properties during expansion at the final stages of spray drying. The wrinkles on the surface of most of the microcapsules is the result of mechanical stresses due to uneven drying at different parts of the liquid droplets during the first drying step. The structure of CLA microcapsules using OSA/XG dried by spray drying showed similar morphologies to the OSA microcapsules alone. This result confirms the XG to OSA ratio has no significant effect on the morphology of spray-dried CLA microcapsules, except for particle size.

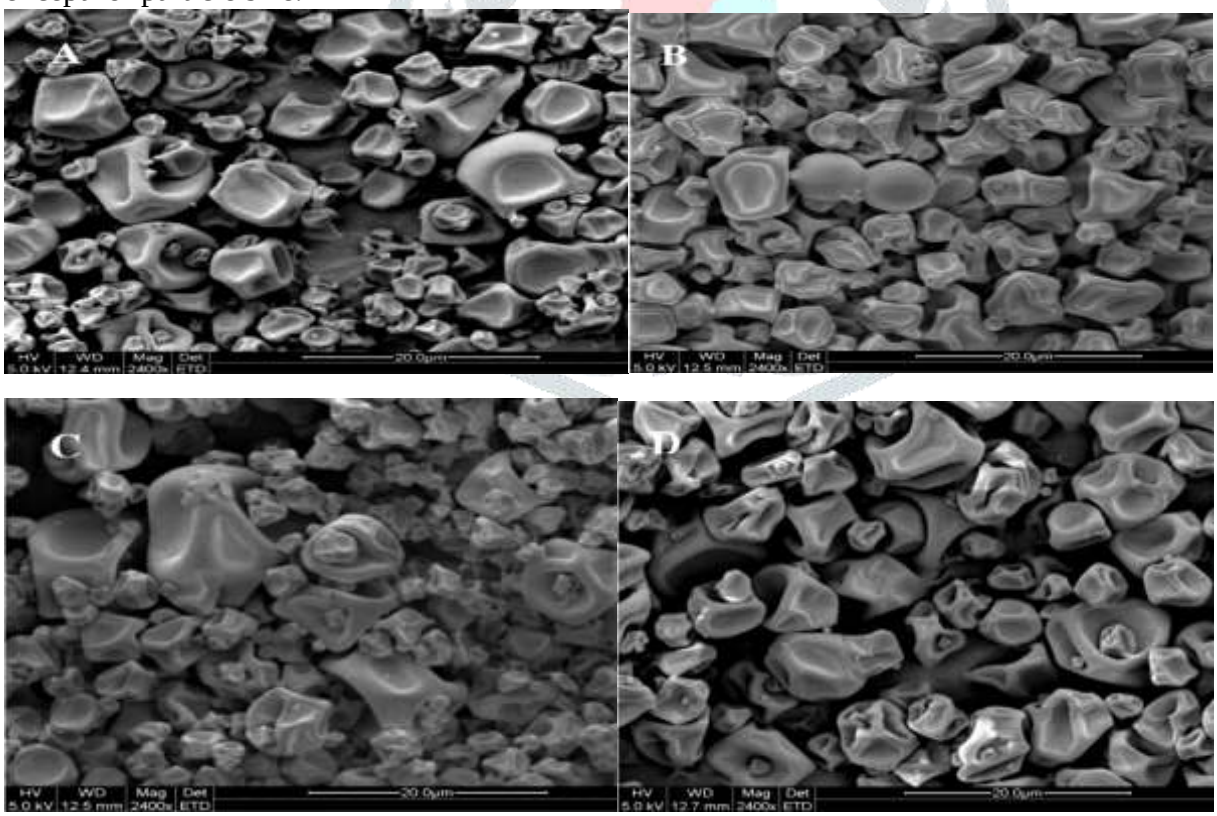


Fig 3.3.3: - Scanning electron microscopy of encapsulated CLA powder made by five different ratios of wall materials. The ratio of OSA and xanthan is (A) 60/1; (B) 80/1; (C) 100/1; (D) Control

3.4 Discussion of Tramadol matrix tablets

3.4.1 Drug release profile –

The effects of XG, XGDSs and CTS on the kinetics of Tramadol release, the dissolution profiles tablets were observed by plotting the cumulative release data/time. During dissolution tests of a hydration in outer layer of matrix tablets during the dissolution test causes swelling and insoluble gelled layer on the matrix outer layer. This gel layer restricts the initial burst effect and slowdown the drug release. Indeed. The 10% of Tramadol was released in the range of 0.62 ± 0.04 to 2.02 ± 0.09 hour (59). The drug release kinetic confirmed that the release rate of tramadol from CTS-XGDS hydrophilic matrices reduced at pH1.2 in the first 2 hours as deacetylation increases, where the amounts of TD release from 16.56% (F2, XGDS1) to 9.95% (F5, XGDS4). When the deacetylation is higher than the resistance of XGSDs-based tablets to the acidic medium was higher. Prolonged increase in dissolution of tramadol was observed reaching 24 hours at pH 6.8 for the formula F5. So, these results showed that effect of deacetylation on the tramadol dissolution profiles**.**

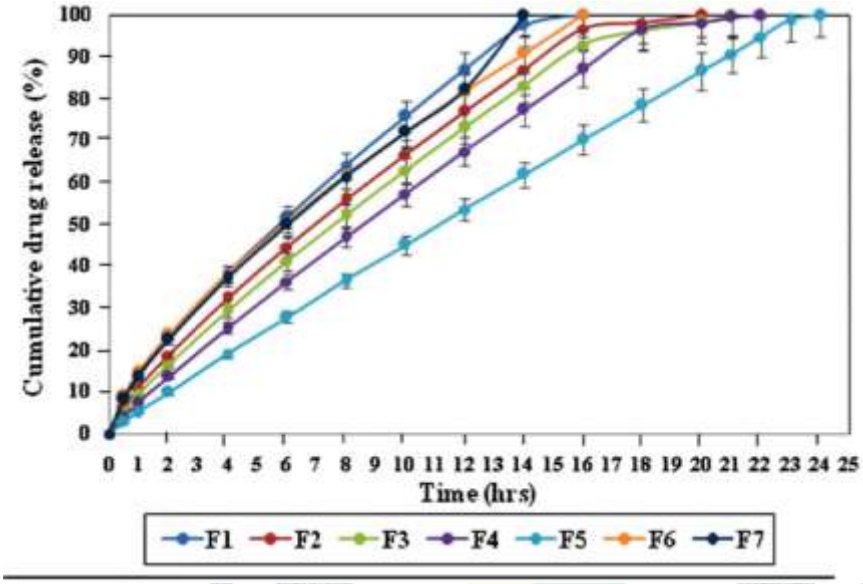


Fig 3.4.1. Drug release profiles of Tramadol matrix tablets (F1-F7).

3.4.2 Thermostability test –

Due to the alkaline deacetylation the thermal characteristics were similar of each sample. The reduction in acetyl group of XG is helpful to reduce steric hindrance & the intermolecular interaction other than that useful to increase the thermal. Analysis of thermograms shows that native XG had two-stage decomposition (60). At first stage 100 % weight loss observed between 0 and 120^{o} C may be caused due to the dehydration. In the case of XG, the second stage above 200^{o}C there is the degradation of the compound due to deacetylation reactions at 540^{o} C with weight loss of 33.33%. In the case of XGDSs, the variation in the second stage of TGA thermograms was due to the variation of polar groups where the weight losses are from 27.80% at 800^{o} C, 28.89% at 758^{o} C, 30.47% at 740^{o} C and 29.68% at 747^{o} C, for XGDS1, XGDS2, XGDS3 and XGDS4, respectively. (6,10,)

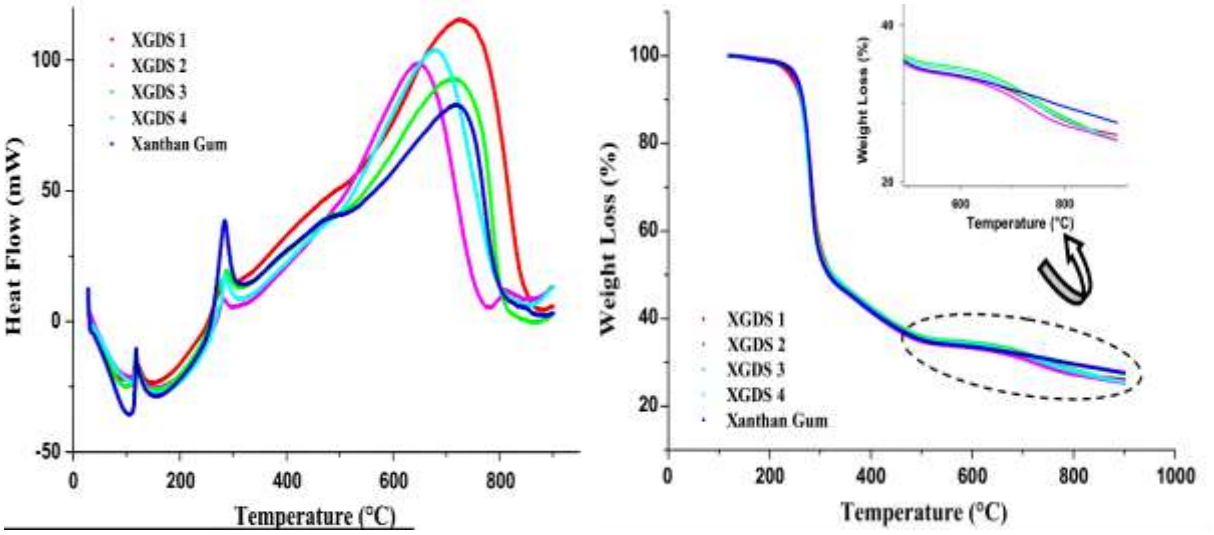
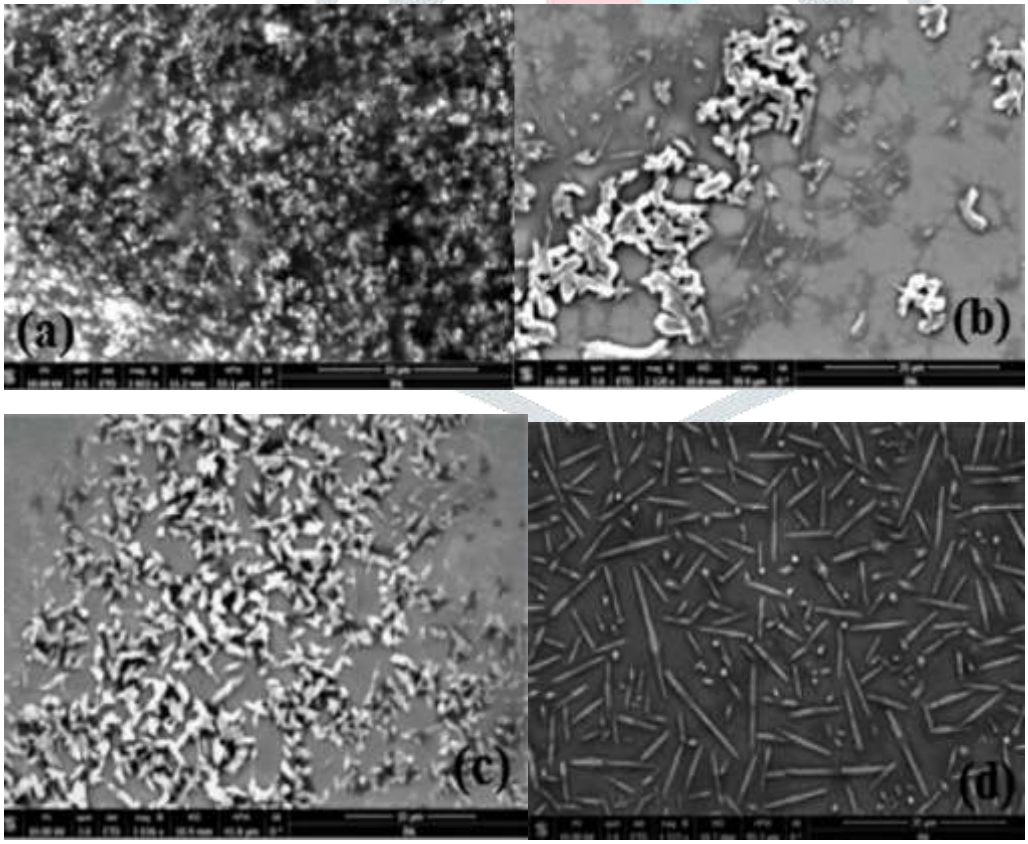


Fig. 3.4.2-a. DSC thermogram curves of native and deacetylated xanthan derivatives
Fig. 3.4.2-b. TGA thermogram curves of native and deacetylated xanthan derivatives.

3.4.3 Morphological characterization

The morphological characteristics of biopolymers are observed by SEM (Fig. a). The significant changes of the surface morphology of XG after reacting showed in obtained data, it showed that XG particles (Fig. b) have an amorphous, porous nature and smooth surface. Whereas of XGDS were having a smooth surface, with an elongated and thin shape, as below (fig. d). The morphology appeared homogenous, indicating a uniform size distribution of XGDS samples.



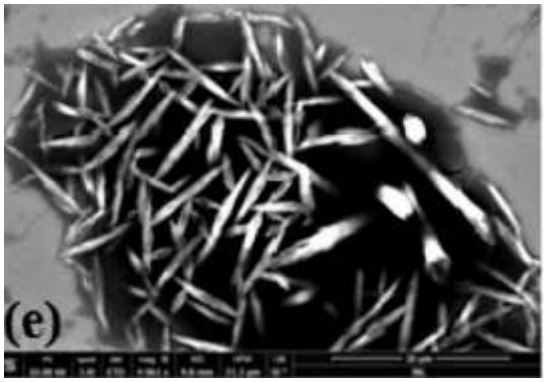


Fig. 3.4.3. ***SEM images at magnification (1000) of (a) native xanthan, (b) XGDS1, (c) XGDS2, (d) XGDS3, (e) XGDS4.***

3.5. Discussion of buccal patches

3.5.1 Weight and thickness of patches: - The weight of mucoadhesive patches were proportionally increased with that of thickness of patches. The ZMT patches were found in the variation of 64–80 mg range. The average thickness of all the mucoadhesive patches ranged from 0.14 to 0.17 mm.

3.5.2 pH measurement: -inner Surface of patch should not be irritable .so the pH measurement is necessary. The pH of the patches comes under the range pH 6.8–7.5 as that same pH of saliva.

3.5.3 Drug content uniformity: - It was determined by UV spectrophotometer at 222.2 nm, the method which was used for the standard curve were repeated for the other patches. The values did not show a significant difference.

3.5.4 Folding endurance**:** - The folding capacity of the patches are important for their strength or prevention from the folding. Endurance of folding is found to be improved with an increasing concentration of PVA and XG. The patches A3, A5 and A7–A9 showed endurance number of folding more than 300.

3.5.5 Tensile strength: - tensile strength is important to identify the stress bearing capacity. Tensile strength increases with the increasing amount of PV.

3.5.6 Swelling property: - patches were started swelling within 5min because of its soluble ingredients, poly vinyl acetate, hydroxymethyl cellulose and xanthan gum.

After 1 hour all patches were got swelled. Formulation A7 containing highest concentration of Xanthan gum 0.3% and lowest concentration of PVA 0.5% that caused highest swelling value. Y1(Swelling index) is as follows: (11,13,23)

$$Y1 = +250.49 + 28.84X1 - 67.86X2 - 16.82X1X2 + 6.18X_1^2 - 7.52X_2^2$$

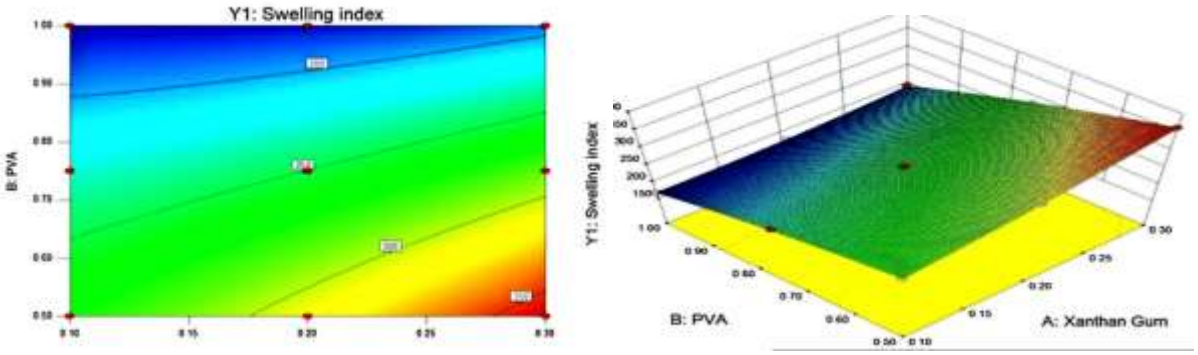


Fig 3.5.6 a. Two- dimensional (2D) contour plot

Fig. 3.5.6 b. Three-dimensional (3D) response surface plots for response Y1 (swelling index) (b).

TABLE 3.5: -

FC	Weight Uniformity(mg)	Thickness (mm)	Surface pH	Drug content uniformity (mg)	Folding endurance	Tensile strength (N/mm^2)	Swelling Index (%)
A1	64±0.057	0.14±0.04	7.39±0.01	2.49±0.01	280±2.51	9.12±0.03	270.48
A2	67±0.050	0.14±0.03	7.22±0.01	2.50±0.02	292±1.00	11.13±0.04	229.2
A3	68±0.036	0.15±0.03	7.33±0.02	2.49±0.03	305±1.52	13.11±0.01	168.79
A4	72±0.050	0.15±0.02	7.02±0.05	2.48±0.01	294±1.52	10.12±0.05	310.78
A5	74±0.050	0.15±0.01	7.12±0.02	2.50±0.01	310±1.52	11.89±0.03	251.34
A6	76±0.032	0.16±0.03	7.13±0.01	2.51±0.01	322±1.52	13.14±0.01	174.32
A7	78±0.047	0.16±0.03	6.83±0.03	2.49±0.03	308±1.52	11.13±0.02	363.60
A8	79±0.037	0.16±0.02	6.93±0.03	2.48±0.01	321±2.08	13.16±0.03	283.30
A9	80±0.040	0.17±0.02	6.85±0.02	2.50±0.02	338±2.51	15.95±0.03	194.61

3.6. Discussion Gx-cl-poly (AA)-MW

Synthesis of semi - INP

The synthesis of semi-Interpenetrating was initiated under irradiation of microwave by thermal initiator APS which causes the formation of sulphate ion radicals Eq. (11). This ion radical SO_4^- further reacts with H_2O molecules of the reaction medium to get OH^- in Eq. (12). the radiation of microwave directly acts to the dipolar ions of water to heating dielectrics then it thermally agitates them to generate radical centers chain. From the hydroxyl groups of Xanthan gum, H^+ were abstracted which causes the process of graft co-polymerization of the monomeric chains onto its equations'. (13), (14). MW of newly formed radical centers acted upon -OH, $–CH_2$. Double bond present on the moiety of monomer of vinyl and generated the polyacrylic acid chains in Eq s. (15), (16).

The propagation step involves the poly-acrylic acid long polymeric chain formation which were further grafted onto xanthan gum backbone Eqs. (17), (18). Further, the polymerization of the grafted chains causes to the presence of some activated centers Eq s. (19), (20). The transformation of long grafted polymeric chains into the 3D crosslinked network were done by glutaraldehyde crosslinking Eq. (21).

Dominance of homo-polymerization over graft co-polymerization which generates into chain termination Eq. (22). Chain reaction also seizes upon disproportionate reaction due to involvement of oxidation and reduction of activated monomeric moieties resulting into the formation of alkane and alkene instead of further propagating the polymerization process Eq. (23) [28].

The mechanism for the synthesis of candidate polymer under MW radiations had been depicted in fig 3.6.1.a.

Step 1 Initiation

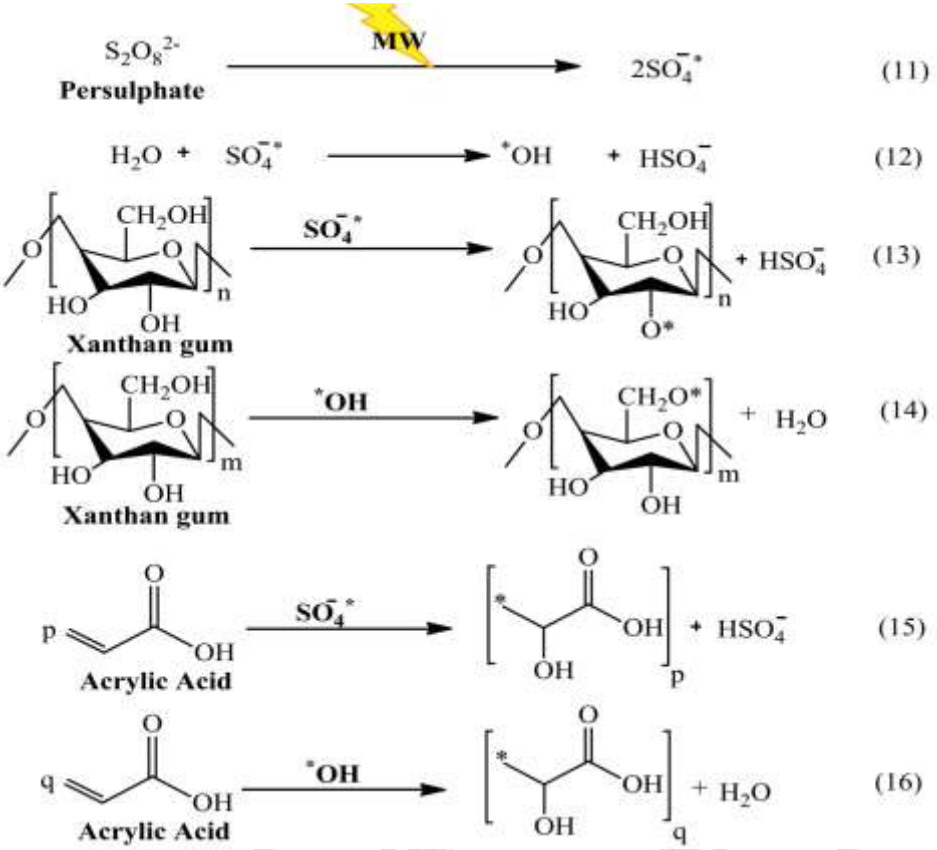
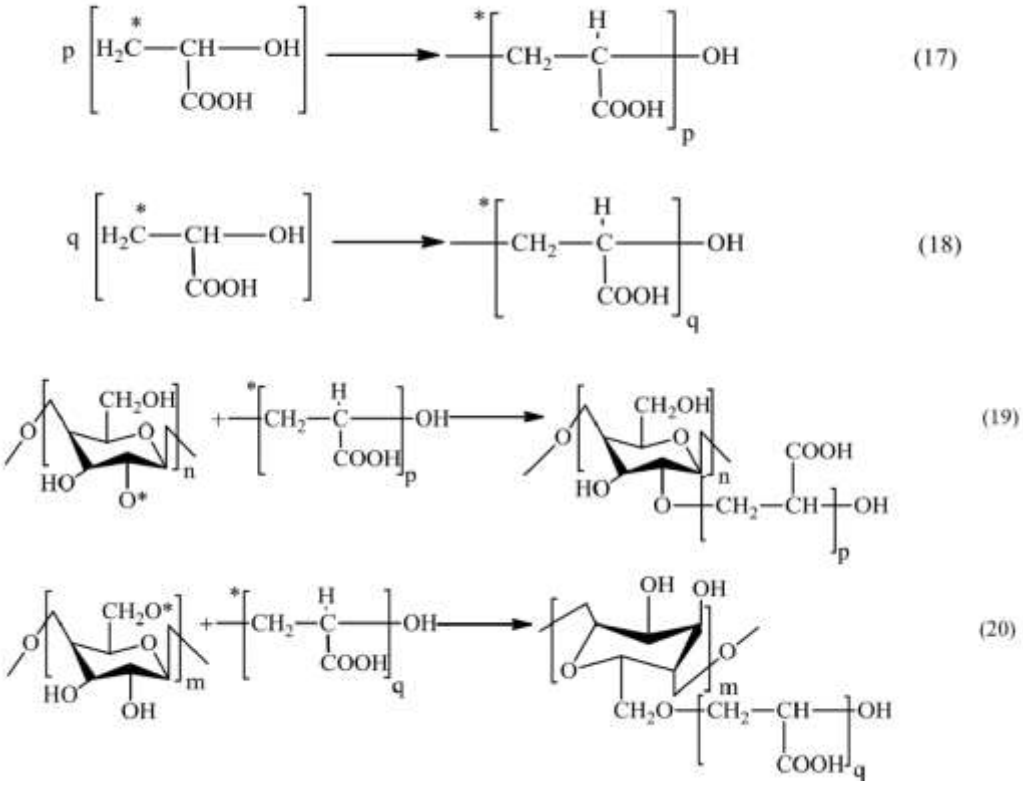


Fig 3.6.1a. chain -initiation reaction

Step 2 Chain propagation



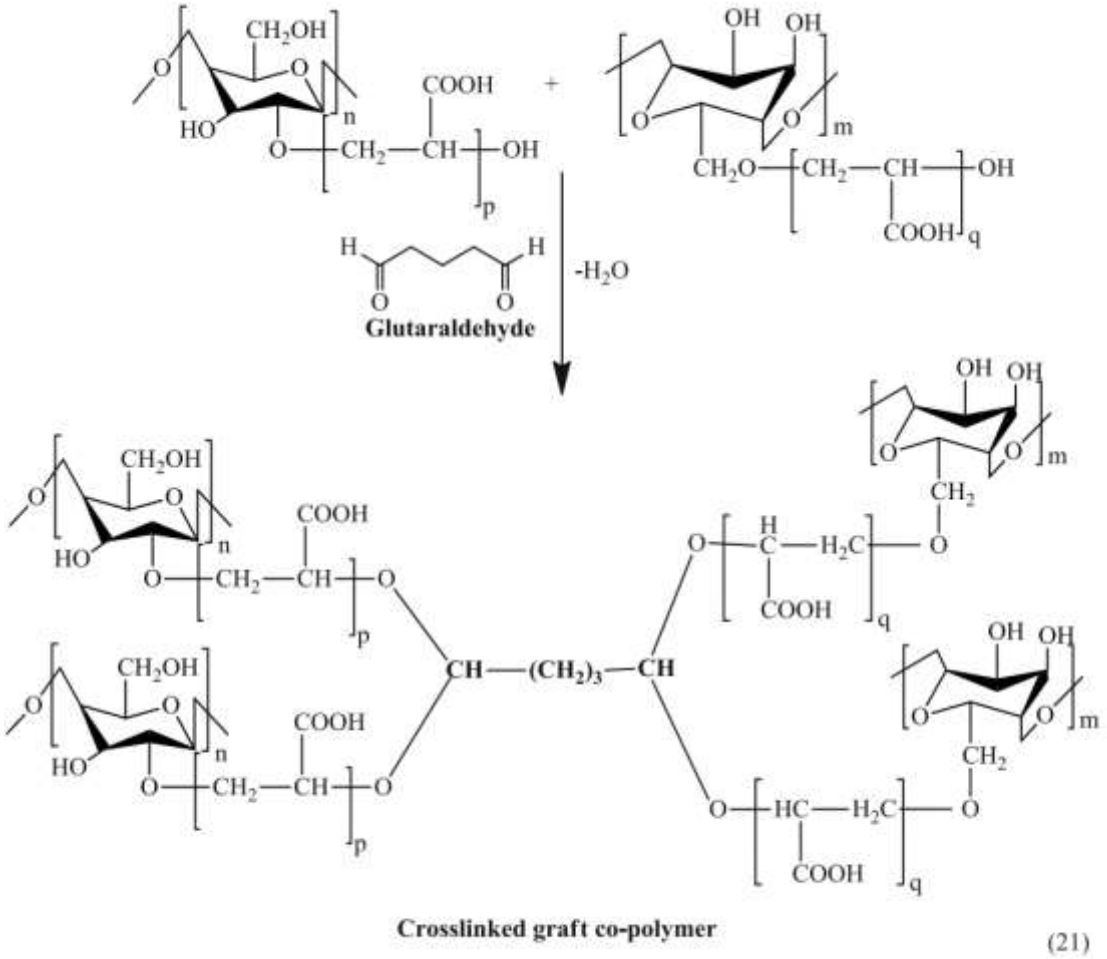


Fig3.6.1. b. chain – initiation reaction

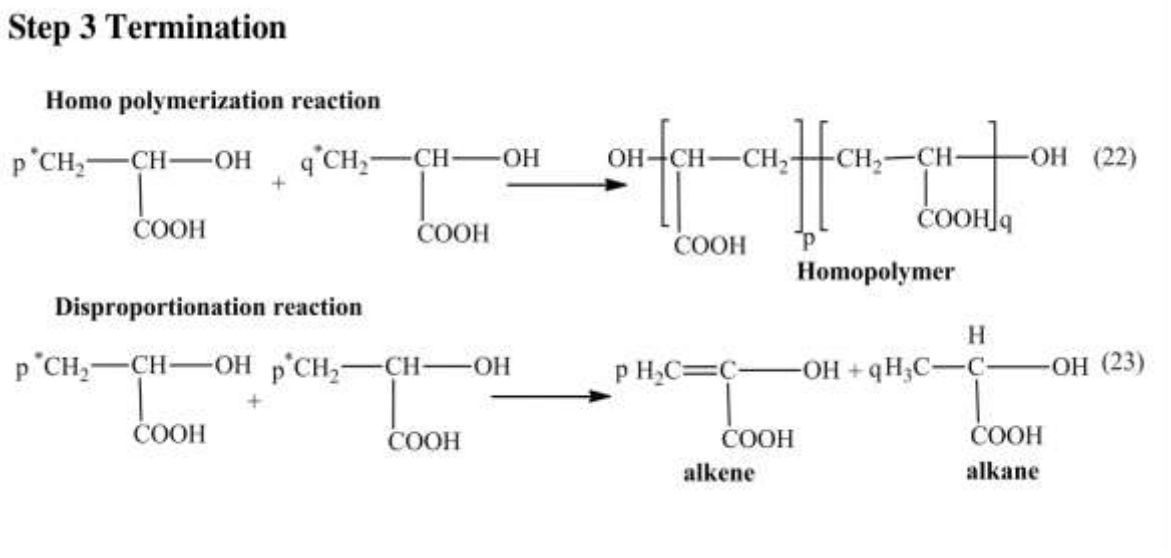


Fig. 3.6.1 c – termination of reaction /synthesis of INP

3.6.2. Swelling studies of the Gx-cl-poly (AA)-

The swelling studies was carried out at different time intervals (4, 8, 12, 16, 18, 20, 24 h), of the candidate polymer with optimized parameters and at different temperature (30, 40, 50, 60, 70 °C) and pH (3.0, 5.0, 7.0, 9.0, 11.0, 13.0) (Fig.). The effect of time upon swelling was examined on the efficacy of fluid uptake of the sample at room temperature and neutral pH. There were found an increase with advent of time and attained maximum value of 522.6% within 24 h, over there were no significant change in Ps value was observed. The increase in Ps value with time could be due to interactions of matrix with solvent prompting molecular relaxation which expanding the matrix but over the level of total complete saturation of the matrix. Further,

the effect of swelling medium temperature on the Ps was examined at neutral pH and time period. The polymer matrix showed the maximum Ps value at 60^{o} C of 857.74%. The efficacy of fluid uptake of the synthesized sample was linearly increasing with increasing temperature up to optimum temperature beyond that point Ps was observed. Further, the influence of swelling medium pH at pre-optimized time and at proper temperature and Ps increases with increase in pH with maxima at pH 11.0 up-to 1079.22% (Fig.). This may be occurred due to ionization of -COOH moieties of polyacrylic acid graft copolymerized onto Xanthan gum backbone along with glucuronic acid residue present on the side chains of backbone.(

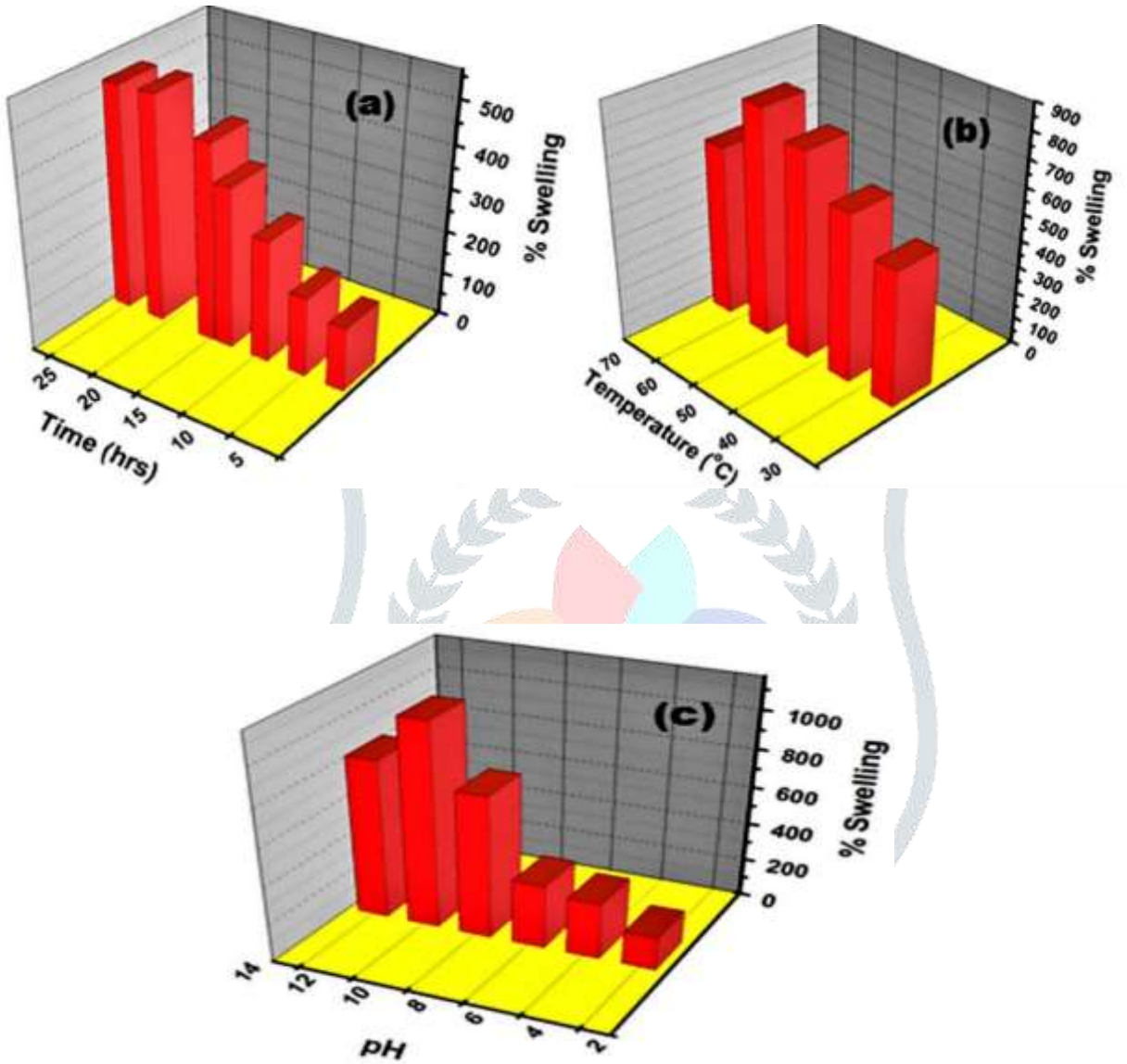


Fig. 3.6.2. a–c: ***Effect on percentage swelling of Gx-cl-poly (AA)-MW with (a) time; (b) temperature; (c) pH of the swelling medium.***

4. CONCLUSION: -

Xanthan gum having some major roles in these formulations. Xanthan gum has vast application in pharmaceutical industries, by the modification, it can be used for the various dosage forms, it has large quantities of (-OH) and (-OOC) in its structure which allows the modification in the structure to improve the quality of xanthan gum. The result shows that combination of xanthan gum and the other polymer improves the efficiency of the dosage form for the sustained release of the drug. Modification with some functional groups enhances the controlled and uniform release of formulation. As in the formulation of microcapsules of anthocyanin the combination of carboxymethyl starch and xanthan gum improves the efficiency and stability from the gastric acid in the stomach and provides targeted release in the intestine of the formulation. This combination enhances the thermal stability of the drug/anthocyanin. In the combination of xanthan gum and

chitosan were very useful for the targeted release of drug without changing the integrity of the chemical nature of drug/ciprofloxacin. Using the modified xanthan gum improves the gelling capacity and swelling property. It improves the uniform release. The deacetylated derivative of xanthan gum shows the good stability and lowering the solubility in water which helps the sustained release of the drug. Modified xanthan gum with chitosan having a good flow property. Deacetylation increases the hydrophobicity which prevents the dissolution and helps from the degradation of drug by GIT. Another combination of xanthan gum and octenyl-succinyl acetate which is used for controlled release of CLA by the process of encapsulation in microcapsules. It protects from the oxidation and drug degradation. Xanthan gum was successfully used in mucoadhesive patches also which provides the tolerability and good stability.

5. **Future prospects-**

xanthan gum is very useful in present as well as in future for dosage forms, in the recent trend it is successfully used for the preparation of novel drug delivery system. It has achieved the success to provide proper drug release at the site of action. It has successfully applied in pharmaceutical industries and other industries and biomedical application. In pharmaceutical industries xanthan gum-based polysaccharides are using as polymer for dosage form, excipients, suspending agent, emulsifying agent. Modified xanthan gum or xanthan gum derivatives are used in the formulations for greater stability and therapeutic value. These modifications are done by addition or substitution on xanthan structure. There are several reactions applying to get maximum ability of xanthan gum for future purpose of optimum treatment.

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