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A REVIEW ON SOURCE, PHYSICOCHEMICAL PROPERTIES, GRADES,PREPARATION, EVALUATION, APPLICATIONS AND PATENTS OF CARBOPOL IN VARIOUS FORMULATIONS

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Abstract:
The current review was prepared with the objectives of complying source, grades, properties, preparation, evaluation, applications and patents of carbopol. Carbopol arepolyacrylic acid polymers which may be used as bio adhesive vehicles for drug delivery.carbopols crosslinked with ally1 sucrose. Materials are available in a number of grades, depending largely on the molecular weight of the polymer chains. Carbopols are thought to be highly polydisperse, with significant differences in the molecular weight of supposedly identical grades reported. Carbopol is widely used in the pharmaceutical industry due to its high viscosity at low concentrations, good patient acceptability, and low toxicity profile. Initially, they were used as an alternative thickening agent to natural gums. Polyacrylic acid (PAA) is a large-scale commercial polymer that is widely used in a variety of industries, agriculture, and medicine. Controlled release in tablets, bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications areall made possible by the readily water swellable carbopol polymers. Thickening at extremely low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams, and gels, oral suspensions, and transdermal gel reservoirs. The prepared carbopol were further characterized for yield FTIR, DSC, XRPD, TGA, SEM, Raman Spectroscopy, Charge density and Zeta Potential.

Keywords: *Carbopol, sustained release, controlled release, polyacrylic acid,*

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INTRODUCTION:

Carbopol polymers were first proposed in 1955 and patented in 1957. These polymers are created using a high molecular weight, crosslinked acrylic acid polymer. Chemically, the carbopol polymer family is similar in that they all have a high molecular weight, crosslinked polymer with polyacryl acid (R. Priyanka *et al.*,2020). Carbopol are polyacrylic acid polymers which may be used as bio adhesive vehicles for drug delivery. carbopols crosslinked with ally1 sucrose. Materials are available in a number of grades, depending largely on the molecular weight of the polymer chains. Carbopols are thought to be highly polydisperse, with significant differences in the molecular weight of supposedly identical grades reported. Carbopol is widely used in the pharmaceutical industry due to its high viscosity at low concentrations, good patient acceptability, and low toxicity profile. Initially, they were used as an alternative thickening agent to natural gums. Subsequent uses include bases for wound dressings ophthalmic vehicles and transdermal systems. Carbopol has been studied as a potential vehicle for an oral bio adhesive system containing chlorhexidine gluconate for dental use (Duncan Q.M. Craig *et al.*, 1994). Carbopols, which are acrylic acid polymers with a very high molecular weight, are generally employed to alter the flow properties of liquid or semi- solid pharmaceutical formulations such gels, suspensions, and emulsions. (Giulia Bonacucina*et al.*, 2004).

Because carbopol 974P NF and 971P NF are polymerized in ethyl acetate, they are a toxicologically preferred alternative to carbopol 934P NF resin. Carbopol 974P, like carbopol 934P, is a highly cross-linked polymer, whereas carbopol 971P is a mildly cross-linked polymer. Carbopol 934P polymeric systems were examined in a variety of propylene glycol and glycerol mixes with a little amount of water added to enable Carbopol neutralisation and to show that adding water to nonaqueous carbopol samples increased their flexibility dramatically (Giulia Bonacucina *et al.*, 2004). Because of their high stability, compatibility, and low toxicity, carbopols are commonly used in cosmetic and pharmaceutical products. Carbopol 934 is a hydrophilic polyacrylic acid polymer, and after neutralisation, its carboxyl groups become highly ionised, forming a gel due to electrostatic repulsion between charged polymer chains (Lu G *et al.*, 1998). The structural features responsible for the interaction between this anionic polymer and mucin were described by Leung and Robinson. Several other studies focused on the effect of polyacrylic acid on ocular contact time and drug bioavailability. The purpose of this study is to gain a better understanding of the factors that influence the interaction between a carbomer viscous eye drop and mucin, and to optimise the eye drop formulation using the information gathered (Jens Ceulemans *et al.*, 2002).

To achieve a high viscosity, it is a weak anionic fluids polyelectrolyte polymer that must be neutralised. Each particle (or network structure) is made up of tightly coiled linear polymer chains that dissolve in polar solvents. The viscosity of carbopol solutions is not affected by the particle size of the powder. When hydrated in water at controlled pH and temperature, thispolymer forms a colloidal dispersion. A carbopol aqueous dispersion is frequently neutralized with a common base, such as sodium hydroxide (NaOH), which converts the acidic polymerinto a salt. When the polymer is neutralised, it has the ability to absorb and retain water. Polymer chains linked by crosslinks begin to hydrate and partially uncoil as a result of electrostatic repulsion to form irreversible clusters. (Kumar K *et al.*, 2014).

The presence of high molecular weight polyacrylate branched chains creates interchain entanglements that prevent flow at low shear stresses, resulting in the desired yield stress nature. Carbopol dispersions' rheological properties have been extensively studied. These properties are determined by the type and extent of crosslinking, which is determined by molecule swelling and medium density (Priscilla R. Varges *et al.*, 2019). Carbopol dispersions are transparent and exhibit significant yield stress and elasticity even at very low concentrations. They have rheological properties that can be tuned by varying both pH and concentration, and they are temperature insensitive. Carbopol has been used as a model material for research into yield-stress fluid properties as well as many fluid dynamics problems such as bubble dynamics, particle settling, and formation. (Park SH *et al.*, 2008).

Rheological studies of carbopol and similar microgels have shown that properties such as concentration and crosslink density determine where they lie on the spectrum between entangled linear polymers and noninteracting hard spheres, with higher crosslink densities and lower concentrations making the system. They noticed that the less crosslinked carbopol 941 became space filling at lower concentrations than the more crosslinked carbopol 940, and based on rheological tests, they determined the crosslink density. Carbopol is a polyelectrolytegel that swells in the presence of ions due to a net outward osmotic pressure (Iris A. Gutowski *et al.*,2012). The pH of Carbopol aqueous dispersions ranges from 2.8

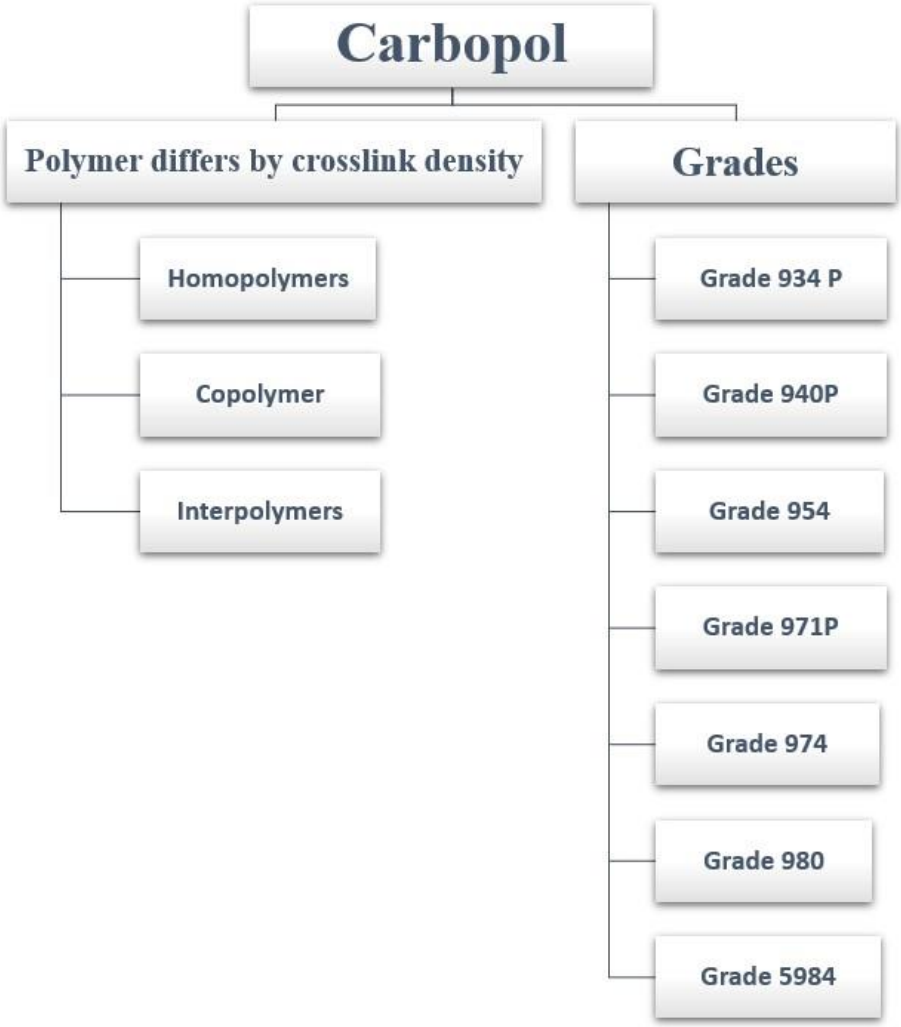
to 3.2, depending on the resin concentration used. In the dry powder state, a molecule of these polymers is tightly coiled into a spiral shape. When a molecule is dispersed in water, it becomes hydrated and slowly unwinds, increasing viscosity. (Sanz Taberner *et al.*, 2002).

One of the most interesting and widely studied swellable systems in controlled drug delivery involves the Carbopol or Carbomer group of polymers. These polymers are cross-linked with allyl sucrose or allylPentaerythritol. Because of the crosslinking, they have a tremendous ability to swell for oral form stable gels. They have been used extensively in topical preparations. Carbomers approved for oral administration as swellable controlled release tablets include Carbopol 934P NF, Carbopol 974P NF, and Carbopol 971P NF.

If any information on the stability of preparations incorporating carbomer as a rate regulatingpolymer is available in the literature, it is quite restricted (V.R. Goskonda *et al.*, 1998). The carbopols are synthetic hydrophilic colloids designed to meet the needs of the cosmetic, pharmaceutical, paint, and related industries for water-soluble resins that can reproducibly thicken, suspend, disperse, and emulsify. (Schoenfeld FK *et al.*, 1958). Carbopol offers an attractive alternative to other poultice materials due to the wide range of organic solvents that can be incorporated into the gel. Carbopol gels have been studied for their effects on sample paper, but references to their use in paper conservation practise are limited to the removal of discoloured natural resin varnishes from historic maps. Carbopol 940 is the brand name for a class of synthetic poly (acrylic acid) polymers that are only partially water soluble. During initial hydration, tightly coiled polymer chains partially uncoil, exposing carboxylic acid groups along the backbone. Protons are removed from these groups when a base is added, partially converting the polymer to a carboxylate salt. Individual chains are straightened by electrostatic repulsions during this process, resulting in a clear, highly viscous gel. (Warda Jet*et al.*, 2007).

The dry white powder polymer contains particles with an average diameter of a few microns that swell to 10 times their initial diameter (1000 times their initial volume) when neutralised. As a result, these particles define the highly cross-linked structure of polymer chains that are surrounded by a solvent, in this case water. The cross-linked chains form small spherical globules less than a micron in diameter as a result of their close packing. As a result, the polymer has a hierarchical structure in which smaller agglomerated particles combine to form much larger spherical entities. The polymer thickening mechanism is depicted. The polymer is highly coiled in powder form, but when dispersed in water, the cross-linked structure begins to uncoil. The extended structure of the polymer network is obtained in the presence of a base, where the reaction between polymer and base leads to ionization along the polymer backbone.(Shafiei M *et al.*, 2018).

Classification of Carbopol:



However, the polymer differs by crosslink density and can be grouped into three categories.
Carbopol Homopolymers: Acrylic acid cross linked with allyl sucrose (or) allyl Pentaerythritol.

Carbopol Copolymer: Mixture of acrylic acid and C-10, C-30 alkyl acrylate related to allyl pentaerythritol.

Carbopol Interpolymers: A carbomer homopolymer or copolymer composed of a polyethylene glycol block copolymer and a long-chain alkyl acid ester. (R. Priyanka *et al.*, 2020).

Carbopol polymers are the various types of Grades:
Carbopol 934: Polymer is a white powder, cross-linked polyacrylic acid polymer. It has short flow properties and a creamy sensory profile, making it ideal for use as a rheology modifier in lotions and creams.
Carbopol 940: It is a highly effective rheology modifier that produces high viscosity and forms sparkling clear gels, hydro-alcoholic gels, and creams. Its non-drip properties and short flow rate make it ideal for clear gels, hydroalcoholic gels, and creams.
Carbopol 971P: Polymer is used in a variety of oral and mucosal contact applications, including extended/controlled release tablets, oral liquids and suspensions, and bioadhesive formulations. It is a lightly crosslinked polymer with a long rheology, resulting in honey-like flow in a semisolid formulation.

Carbopol 954: Polymer was developed as a benzene free replacement for Carbopol 934. It iscurrently used in Crest toothpaste formulations.
Carbopol 974P: Oral liquids, bioadhesive formulations, oral care formulations, and extended-release tablets are among the applications for which polymer was introduced.

Carbopol 980: Polymer is a white powder composed of crosslinked polyacrylic acid that has been polymerized in a toxicologically acceptable cosolvent system. It is a highly effective rheology modifier that produces high viscosity and forms sparkling clear gels, hydro-alcoholicgels, and creams.

Carbopol 5984: Polymer is a white powder that is cross-linked polyacrylic acid polymerized in a toxicologically preferable cosolvent system. It's a powdered Carbopol polymer with very low viscosity at less than 0.2 percent and very high viscosity at greater than 0.5 percent. (Giulia Bonacucina *et al.*, 2004).

Structure of carbopol:
Poly (acrylic acid) (PAA) is widely used as a superabsorbent polymer. (J. Loiseau *et al.*, 2003). Poly (acrylic acid) (PAA; trade name Carbomer) is a polymer with the formula $(CH_2\text{-}CHCO_2H)_n$. PAA, its salts, and PAA-based polymeric materials are used as emulsifiers and thickeners in aqueous solutions and dispersions of both natural and synthetic latexes, as well as smoothing agents in synthetic fibres, sorbents and ion exchangers, aqueous quenching media, flocculants, plastics, etc (Magdy Y. Abdelaal *et al.*, 2012). It is a derivative of acrylic acid (CH_2=$CHCO_2H$). Aside from homopolymers, a variety of copolymers and crosslinked polymers, as well as partially deprotonated derivatives, are known and commercially valuable. PAA is an anionic polymer in water at neutral pH, which means that many of its side chains lose their protons and acquire a negative charge. PAAs that have been partially or completely deprotonated are polyelectrolytes that can absorb and retain water and swell to many times their original volume. PAA is produced by free radical polymerization. Initiatorsinclude potassium persulfate and AIBN. PAA is commonly used in dispersants, and the molecular weight has a significant impact on the rheological properties and dispersion capacity, as well as the applications. In 2008, approximately 1,600,000,000 kg were produced. (Ohara, Takashi *et al.*, 2003). Polyacrylic acid is a weak anionic polyelectrolyte whose degree of ionisation is affected by the pH of the solution. At low pH, PAA can form hydrogen-bonded interpolymer complexes with a variety of non-ionic polymers (including polyethylene oxide, poly-N-vinyl pyrrolidone, polyacrylamide, and some cellulose ethers). (vitaliy V khutoryanskiy *et al.*, 2009).
The synthesis of PAA and its properties have been extensively researched and reviewed. Some important points will only be mentioned briefly. PAA is made by polymerizing acrylic acid (AA) with photo initiators or under the action of γ-radiation. When exposed to UV radiation in its solid state, AA converts to polymer. In aqueous solution, hydrogen peroxide, alkali metal or ammonium persulfates, and cumene hydrogen peroxide start the polymerization of AA. Only non-ionized AA molecules enter the polymerization reaction, and the reaction rate is kept to a bare minimum. (Magdy Y. Abdelaal *et al.*, 2012).

A polyolefin is polyacrylic acid. Polyethylene with carboxylic acid (CO_2H) substituents on alternating carbons is what it is. Alternating carbon atoms in the backbone are stereogenic as a result of these groups (colloquially: chiral). As a result, although this aspect is rarely discussed, acrylic acid exists in atactic, syndiotactic, and isotactic forms. Polymerization begins with radicals and is assumed to be stereorandom. Crosslinking can be introduced in a variety of ways. (Ohara, Takashe *et al.*, 2003).

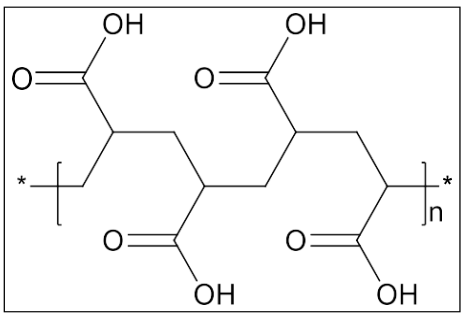


Fig 1: Structure of carbopol

Chemical structure of a) acrylic acid and b) poly (acrylic acid). (Fahmy A et al., 2011). Carbopol polymers are offered as fluffy, white, dry powders (100% effective). Many of the product's advantages are due to the carboxyl groups provided by the polymer's acrylic acid backbone. Carbopol polymers have an average equivalent weight of 76 per carboxyl group. (Panzade P et al., 2010).

Mechanisms:

This polymer's molecule is tightly coiled in the dry powder state, limiting its thickening ability. When the molecule is dispersed in water, it begins to hydrate and uncoil slightly, causing the viscosity to increase. The molecule, however, must be completely uncoiled in order to achieve the best possible performance from the polymer. The molecule can completely uncoil in two ways, providing maximum thickening, emulsion formation and stabilization, or bioadhesion performance. The most common mechanism is to use an appropriate base to neutralise the polymer. During neutralisation, the carbopol polymer ionises, resulting in negative charges along the polymer backbone. Due to the repulsion of likenegative charges, the molecule completely uncoils into an extended structure. This reaction isquick, and it yields effective results. This is simple to do with sodium or potassium hydroxide or amine bases such as Tris (tris (hydroxymethyl) aminomethane). To neutralise less polar ornon-polar solvent systems, only amines should be used. In a second thickening mechanism, a hydroxyl donor is used. When a carboxyl group and one or more hydroxyl donors are combined, hydrogen bonds form, resulting in thickening. Maximum thickening can take anywhere from five minutes to several hours due to the time-dependent nature of this mechanism. The pH of such systems is typically acidic. Polyols (glycerine, propylene glycol, PEGs, and others) and sugar alcohols (mannitol, sorbitol, and others) are common hydroxyl donors, as are non-ionic surfactants with 5 or more ethoxy groups and others. (Panzade P *et al.*, 2010). In case of drug release mechanism carbopol polymers are efficient matrix-forming excipients. These polymers are not soluble and are swellable in water. Other hydrophilic controlled-release excipients, such as hydroxypropyl methylcellulose, on the other hand, are linear polymers that are not chemically crosslinked and thus water-soluble. The drug is dispersed homogeneously throughout the polymer matrix. Drug release from tablets and capsules with carbopol polymers is controlled by:

Drug diffusion occurs through the gel layer formed by the polymer when it comes into contact with the aqueous medium.

Relaxation of the matrix (polymer).

The following happens when carbomer tablets come into contact with the dissolution medium:

A drug in the outer layer exposed to the bathing solution dissolves and diffuses out of the matrix; and

• The polymer swells to form a hydrated matrix layer (hydrogel). Because of the crosslinked nature of the polymers, the hydrogel is made up of discrete microgels made up of many polymer particles in which the drug is dispersed rather than single entangled chains of polymers (as is the case with linear polymers).

The hydrated matrix layer controls water penetration (into the non-hydrated core) and diffusion of the drug through the hydrated matrix. (https://www.lubrizol.com/-/media/Lubrizol/Health/Literature/Carbopol-Formulation-and-Processing-Guide-for-Oral- Solid-Dosage-Forms.pdf)

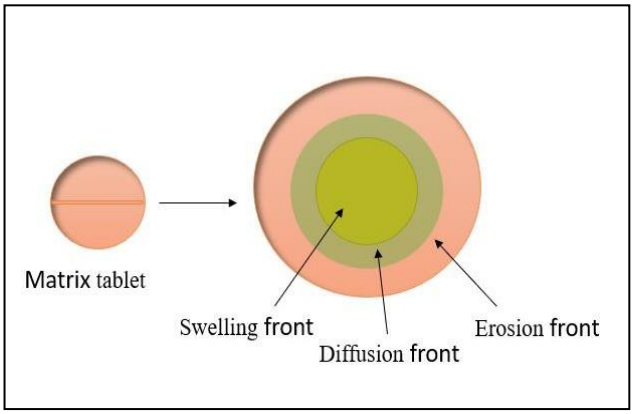


Fig 2: -Drug release schematic

Properties of Carbopol: (Park A.,2006., Panzade P., 2010, Goskonda VR.,1998, http://www.thegoodscentscompany.com/data/rw1275751.html., https://www.lubrizol.com/-/media/Lubrizol/Health/TDS/TDS-730_Viscosity_Carbopol_in_Aqueous-Systems.pdf)

Physicochemical Properties	Description
Physical state	Solid, anhydrous to hydrated material.
Structure	Synthetic high molecular weight polyacrylic acids cross linked with allyl sucrose or allyl pentaerythritol
Appearance	Fluffy, white, mildly acidic polymer
Molecular weight	713.1
Colour	White
pH value	6.0-7.0
Boiling point	116ºC
Refractive Index	1.33
Relative Density	1.2 g/ml at 25° C
Specific gravity	1.41
Bulk density	Approximately 208 kg/m3 (13 lbs. ft3)
Melting point	95 °C
Particle size	0.2 micron
Specific Surface area	57.5 m^2/g
Vapour pressure	3.423000mm/Hg 25.00ºC
Solubility	After neutralisation, it swells in water, glycerin, and ethanol (95 percent). Carbomers, which are three- dimensionally crosslinked microgels, do not dissolve but swell significantly.
Storage	Keep container tightly closed, keep in a cool, well-ventilated place
Chemical stability	Stable
Compatibility	Compatible with anionic, Non-ionic and cationic surfactant
PKa	6.0 ± 0.5
Moisture content	2.0% maximum
pH of 1.0% water dispersion	2.5 - 3.0
pH of 0.5% water dispersion	2.7 - 3.5
Equivalent weight	76 ± 4

Carbopol Manufacturing and Grading:
Carbopol polymers are created through a cross-linking process. Various grades of carbopol are available, depending on the degree of cross-linking and manufacturing conditions. Each grade has its own significance in terms of its usefulness in pharmaceutical dosage forms. Carbopol 934 P is polymerized in benzene after being cross-linked with allyl sucrose. Carbopol 71G, 971 P, and 974 P are polymerized in ethyl acetate after being cross-linked with allyl pentaerythritol. Polycarbophil is a cross-linked polymer that is polymerized in the solvent benzene. All ethyl acetate-based polymers are neutralized with 1-3 percent potassium hydroxide. Despite the fact that Carbopol 971 P and Carbopol 974 P are manufactured by the same king agent as Carbopol 974 P. Carbopol 71 G is the granular version of the Carbopol grade (Panzade P *et. al.*, 2010).

Preparation of Carbopol:
Non-neutralized gels of 0.25 percent w/v C974P were made by gradually dissolving the polymer powder in water for 30 minutes while continuously stirring the solution. Sorbitol or mannitol is pre-mixed with Carbopol powder in the solid state before being added to water. After complete solubilization, the solution is stirred for at least 2 hours. The pH is then adjusted to 7.4 with 0.1M NaOH using a WTW ino Lab pH 730 pH metre equipped with a glass/platinum combined electrode (Pauline Lefrancois *et.al.*, 2015).

PH of Carbopol gel:
The pH of the carbopol gel was measured by pH meter, Mettler Toledo-MP 220, 1g of carbopol was dispersed in 50 ml of distilled water with vigorous stirring with a glass rod untilthe pH of the gel became constant, which may take about 3 min. The pH of carbopol gel wasfound to be 5.5–6.6 (Maslii Y *et. al.*, 2020).

FTIR study of Carbopol:
FTIR study was done for the functional group detection in a sample and to study interaction in the complex samples. For the FTIR spectra, the sample of 2 mg was thoroughly mixed with the 100 mg dry Potassium Bromide (KBr) in a mortar and molded into pellets made by the hydraulic press applying a pressure of 5 tons The FTIR spectra were recorded using FTIR (8400S Shimadzu, Tokyo, Japan) in the range of 400to 4000cm^{-1}.

The FTIR study of carbopol spectra showed a peak in the 3000-2950 cm^{-1} range, representing OH stretching vibration, i.e., υO-H and intramolecular hydrogen bonding. The prominent peakbetween 1750 and 1700 cm^{-1} was assigned to carbonyl C = O stretching band i.e., υC = O whilethe peak at 1450 to 1400 cm^{-1} was for υC-O/δ O-H. The band at 1250 to 1200 cm^{-1} suggested υC- O-C of acrylates. The ethereal crosslinking represented a stretching vibration of the C-O-C group, as indicated by the prominent peak at 1160 cm-1. The band between 850 and 800 cm- 1 suggested out of plane bending of C = CH, i.e., aromatic ene bending vibration. (Sahoo S *etal.*, 2011).

Table No.1 Prominent FTIR Peak of Carbopol

3000-2950	Hydroxyl group	O-H stretching vibration, intramolecular H-bonded
1750-1700	C = O group of acid	υC = O stretching vibration
1450-1400	Carbonyl group of acids	C-O stretching vibration
1250-1200	Acrylates	C-O-C stretching vibration
1160	Ethereal C-O-C group	Stretching vibration of C-O-C group
850-800	Aromatics and enes	= C-H out of plane bending vibration

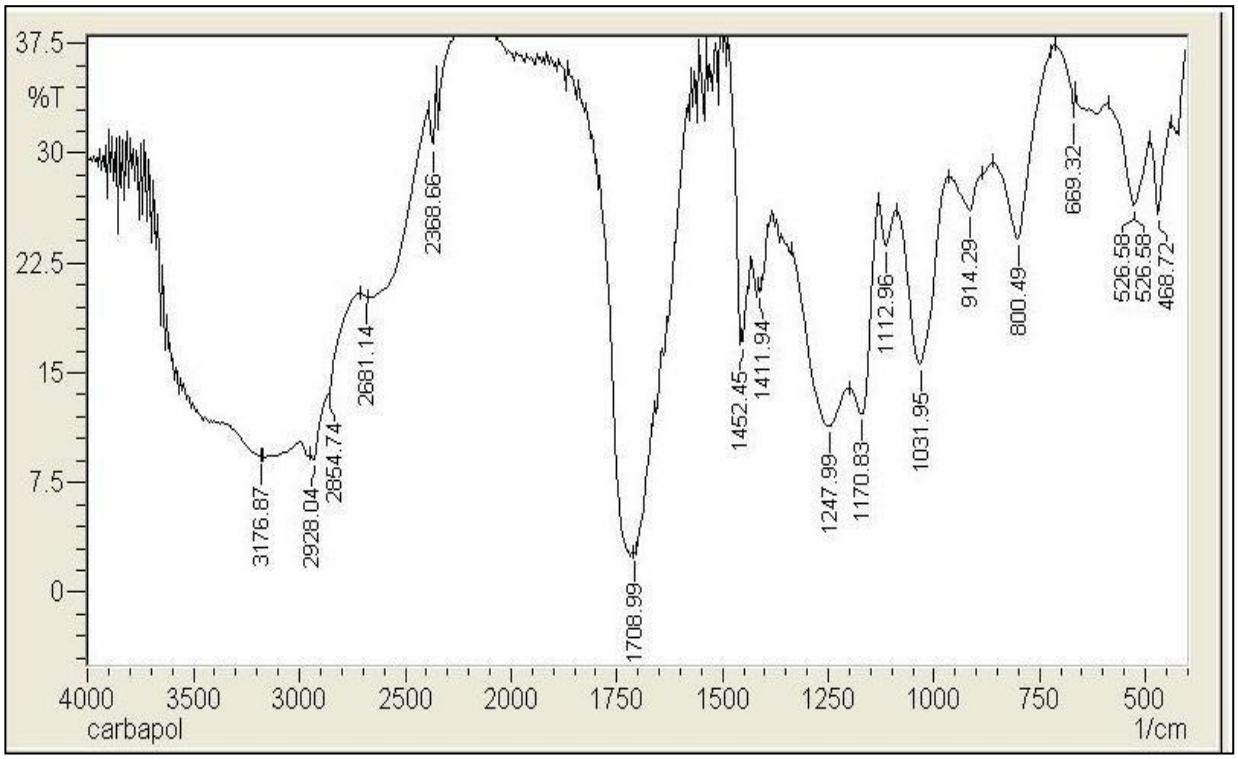


Fig 3: FTIR spectra of Carbopol

Thermogravimetric Analysis (TGA): The TGA of carbopol assigns the weight loss at threedifferent steps at first, a 10% weight loss is observed at 100 C, followed by a loss of moisture;then, as the temperature rises to 320 C, a weight loss of 23% is observed due to decarboxylation, the development of unsaturated structures, and the polymer's depolymerization; finally, carbopol degradation begins at 400 C and continues until completely paralysed. (Suhail M *et al.*, 2020).

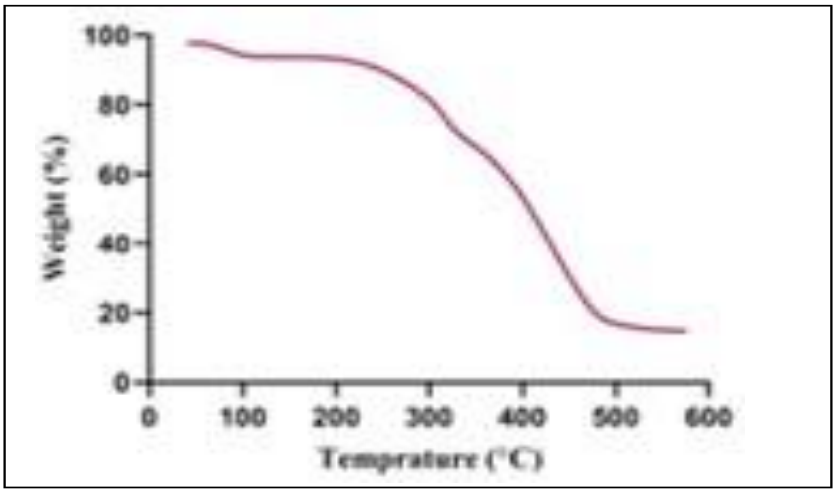


Fig 4: TGA of carbopol

DSC (Differential scanning calorimetry):
Glass transition temperature (Tg) was observed near 120-140 0C in the DSC thermogram of Carbopol 971P. Carbopol 971P decomposition was observed near 280-300 0C, where Carbopol melted and decomposed sequentially. The endothermic peak at 80-100 0C was due to physically bound water (Hosmani AH *et al.*, 2013).

Charge density and Zeta-potential of carbopol:
Charge on carbopol particles can be determined by differential light scattering by measuring zeta potential value. Zeta potential indicates the surface electrical charge on the particles and indicating the physical stability system, which was measured by determining the electrophoretic mobility using the Malvern Zetasizer (Nano ZS 90, Malvern Ltd, Malvern UK) (Ismail SH *et al.*, 2021).

The zeta-potential measurement of the carbopol, 0.5 g of carbopol dispersed into the 500 ml of aqueous 0.01 M KNO3 solution at 25^0C. A 1 mL supernatant after conditioning was transferred to the zeta potential cell, which was loaded to the machine, and measurement was performed by Malvern Zetasizer (Nano-ZS 90). The Zeta potential of -30.3 mv was observed in the Zetasizer. Which shows the large negative electric charge potential at the surface. That indicates clay particles have a large potential for extensive binding of cationic drugs (Andonova V *et al.*, 2014).

Scanning Electron Microscopy of carbopol:
The morphology of samples was determined using a scanning electron microscope (SEM) (HITACHI S-3000N, Japan) set to 20 kV (filament current of 1.75 A, beam current of 30–40 mA, and probe current of 250 pA). Mounting 0.5 mg of powder onto a 5 mm 5 mm silicon wafer affixed to an aluminium stub with graphite tape yielded the samples. The powder was then sputtered-coated with a 200 layer of gold/palladium alloy for 40 seconds at a beam current of 38–42 mA (Sahoo S *et al.*,2011).

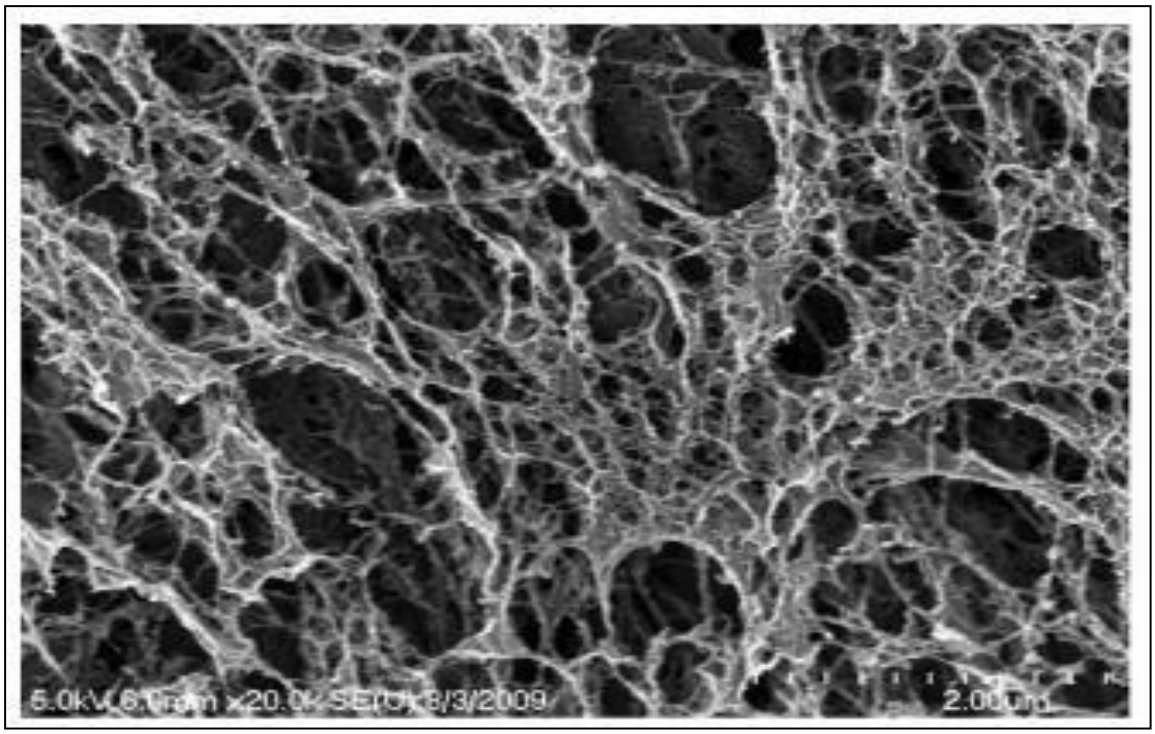


Fig 5: SEM image of Carbopol

Raman Spectroscopy:

The Raman system R-3000 instrument, manufactured by Raman systems INC.USA, is a low- resolution potable Raman Spectrometer with a 785 nm solid state diode laser adjusted to deliver 250 mw to the sample and spectral resolution of 10 cm^{-1}, as well as 12 v dc/5A power supplies and USB connectivity. This Raman Spectrometer is equipped with a fibre optic sampling probe, A safety shutter, as well as automatic focusing caps for both solid and liquid samples, are included. The solid powder samples, which were pure polymers, were sealed inplastic poly bags and tested at room temperature. Outside light interference was also prohibited in order to avoid photon shot noise. The spectra were collected from 140 to 2500 cm^{-1} in wave number range.

In case of C940, the prominent bands were found at 337, 523.89, 876.80, 1366.5 and 1687.5 cm^{-1} The bending vibration of C-C-O group was indicated by the Raman shift at 523.89 cm^{-1}. The band at 876.80 cm^{-1} was assigned to stretching vibration of (C-O-C) of acrylates. The Raman shifts at 1366.5 cm^{-1} and 1687.5 cm^{-1} are the characteristics for the symmetric stretching vibration of O-C-O and carboxylic group (C=O) of acids (Sahoo S *et al.*,2011).

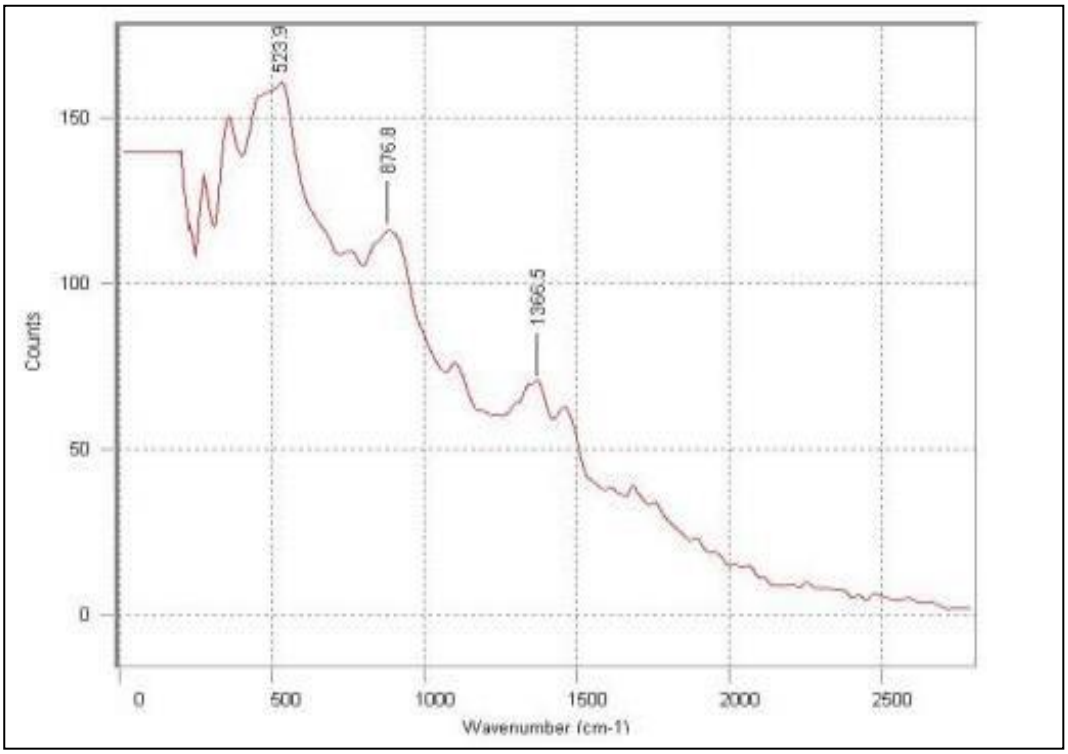


Fig 6: Raman Shifts of Carbopol940 (C940)

Ray Diffractometry:

The XRD measurements were performed on a Philips X'Pert powder diffraction system (Philips Analytical, The Netherlands) outfitted with a vertical goniometer in the Bragg- Brentano focusing geometry. The X-ray generator was set to 40 kV and 50 mA, and the radiation source was the Cu K line at 1.54056. Each powdered specimen was placed in a glass specimen holder. The specimen and apparatus were set up with coplanarity of the specimen surface with the specimen holder surface and the specimen holder set at the position of symmetric reflection geometry. The powders were sieved through a 100mesh sieve before being placed in the sample holder using the side drift technique. The holder was made up of a central cavity. In order to make a sample, A glass slide was clipped to the top face of the sample holder to form a wall for analysis. The powder sample was placed in the holder, gently tapped, and subjected to XRD analysis. Using an automatic divergence slit assembly and a proportional detector, 10 mg of each sample was scanned at 25°C from 10 to 70 (2), with a step size of 0.020 and a count time of 2.00 s. Strip chart relative intensities were read and corrected to fixed slit values. The powder X-ray diffraction patterns for the pure C940 figure. The Carbopol polymers were found to show similar XRD patterns (Figure)m (Sahoo S *et al.*,2011).

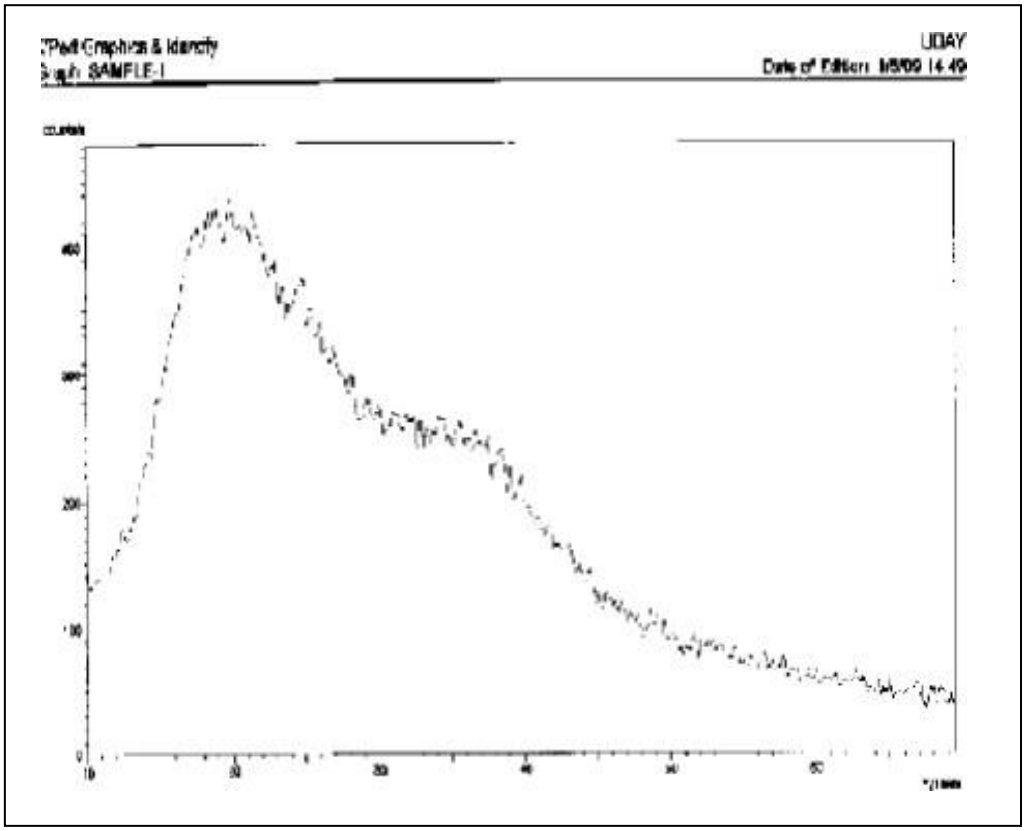


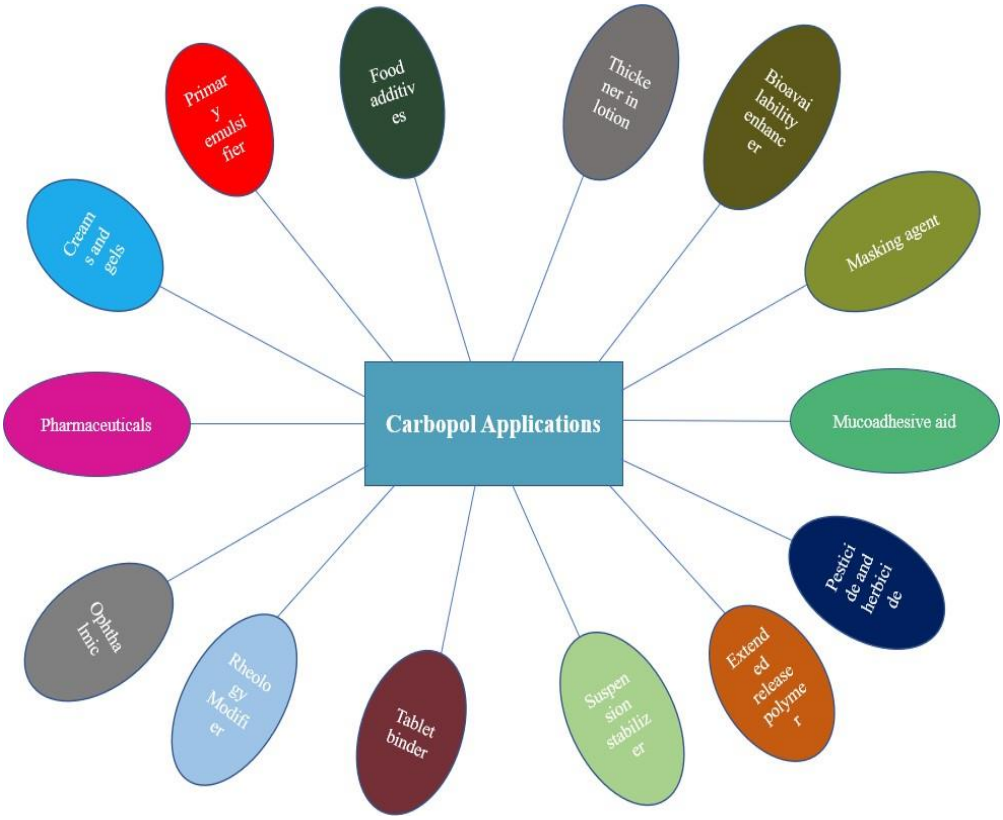
Fig7: X-ray diffraction of Carbopol

APPLICATIONS OF CARBOPOL POLYMERS:

Polyacrylic acid (PAA) is a large-scale commercial polymer that is used in many industries, including agriculture and medicine. The readily water swellable carbopol polymers enable controlled release in tablets as well as bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal, and rectal applications. Thickening at low concentrations to produce a wide range of viscosities and flow properties in topical, lotions, creams, and gels, oral suspensions, and transdermal gel reservoirs. Because of its properties, carbopol has the potential to be useful as a pharmaceutical excipient in a variety of applications, including:

Controlled release and solid dosage forms:

Since the last four decades, carbopol has been used in controlled release solid dosage formulations. In recent years, the number of manufacturers commercializing controlled release tablets based on carbomers has increased significantly. Carbopol polymer-based tablet formulations have demonstrated zero-order and near-zero-order release kinetics. At low concentrations, these polymers are effective (less than 10 percent). Nonetheless, they exhibit extremely rapid and efficient swelling in both simulated gastric fluid (SGF) and simulated intestinal fluid (SIF). Carbopol polymers yield tablets with high hardness and low friability. These polymers can be successfully formulated into a variety of tablet forms, including traditional swallowable tablets, chewable tablets, buccal tablets, sublingual tablets, effervescent tablets, and suppositories, while providing controlled-release properties and good binding properties (Panzade P *et al.*, 2010).



Carbomers dissolve faster at lower concentrations than other excipients. Because of these factors, carbopol polymers are more widely used in the formulation of dosage forms. Because Carbopol polymers swell rapidly in water and absorb a large amount of it, roller compaction is being used to prepare a new form of Carbopol polymer 71G NF in order to avoid the use of flammable solvents. Carbopol polymer 71G NF is a useful and versatile controlled-release additive for direct compression tablet formulations. (Panzade P *et al.,* 2010) (S Ishikawa *et al.,* 1987). As a result, carbomers serve as effective controlled release agents for matrix tablets while also improving drug bioavailability. As the only granular polymer (Carbopol 71G NF) available for direct compression formulation, they act as efficient binders in both dry and wet granulation processes.

Oral Suspension Applications:

Carbopol polymers have been widely used in oral suspensions for many years to thicken, change flow properties, suspend insoluble ingredients, and provide bioadhesion. These polymers are significant because they eliminate the settling problem even at low concentrations. When Carbopol polymers are hydrated and neutralised, they swell and form colloidal dispersion. They are highly efficient at low levels and provide long-term suspension stability across a wide pH range. They can also be used to increase viscosity and mask the bitter taste of certain drugs. (Mou-ying Fu Lu *et al*., 1990) (A. Delgad *et al.,*1990)

Bioadhesive Applications:

Many hydrophilic polymers cling to mucosal surfaces by attracting water from the mucus gel layer adhered to the epithelial surface. This is the most basic adhesion mechanism and has been labelled "adhesion by hydration." At the molecular level, mucoadhesion involves various types of adhesive force, such as hydrogen bonding between the adherent polymer and

the substrate, i.e. mucus. (Anlar *et al.*,1993). Carbopol polymers have been shown to form a strong bond with the mucus membrane, resulting in strong bioadhesion. Many commercial oral and topical products on the market today and in development have been formulated withCarbopol polymers, which offer numerous advantages in bio adhesive formulations. They improve patient compliance by lowering the concentration of active ingredient and increasing the bioavailability of certain drugs in addition to having excellent adhesion forces.

Topical applications:
Because carbomers are non-sensitizing and have no effect on drug biological activity, they are well suited to aqueous formulations of topical dosage forms. They have good thickening, suspending, and emulsifying properties for topical formulations.

Products with a wide range of viscosities and flow properties have been successfully formulated and commercialized. Carbopol polymers are used to keep active ingredients suspended in transdermal reservoirs, as well as topical gels and creams. (Gumma A *et al.*, 1971), (Panzade P *et al.*, 2010)

Oral Care Applications:
Carbopol polymers give toothpaste formulations desirable properties such as viscosity, yieldvalue, low thixotropy, and clarity. The primary function of polymers is to impart viscosity at very low concentrations to thicken a system. Suspension of abrasives and solid actives is achieved by increasing yield value at low polymer concentrations. The ability of carbopol polymers to build yield value in combination with low thixotropy results in a clean, non-stringing ribbon of toothpaste. This means that Carbopol toothpaste formulations are pumpable, leave minimal solids residue on the tube rim, hold up well on the brush, and can be used in clear formulations. (D Laba et al., 1993) (Panzade P *et al.*, 2010)

Taste Masking Application of Carbopol:
Carbopol polymer is widely used in the formulation and development of taste masked bitter active pharmaceutical ingredients, because more than 50% of pharmaceutical formulations have a bitter taste and it is necessary to mask the bitter taste with a suitable method for patientconvince and pediatric patients. As a result, carbomer-934 and carbomer-970 were used to mask the taste. Carbomer-934 drugs form a complex through kneading and microencapsulation, and after taste testing, the complexes are formulated into tablets and evaluated. (Pérez-Marcos B *et al.*, 1991).

Regulatory Status of Carbopol Polymers:
Carbopol polymers, Pemulen polymeric emulsifiers, and Noveon polycarbophils have all been thoroughly reviewed and tested for toxicity. Both Noveon polycarbophils and calcium polycarbophils are GRAS (Generally Recognized as Safe) materials. Noveon, Inc. has also determined that Carbopol 934, 934P, 971P, and 974P are GRAS when used in vitamin tablets (assumes a use level of our products ranging from 8% to 30% of tablet mass, with a typical use of 15% to 20%; the average weight of the vitamin tablet is 500 mg based on information from the Physician's Desk Reference, 48th Edition, 1994). The Cosmetic Ingredient Review Expert Panel summarized the toxicity of Carbopol polymers in their assessment of the safety of Carbopol polymers for cosmetic ingredients. This assessment, as well as subsequent toxicology testing, revealed a low toxicity and irritation potential. Polymers have gained widespread acceptance in a variety of pharmaceutical, cosmetic, and detergent applications as a result of extensive testing and the properties they provide (Berney BM *et al.*, 1979).

PAA's primary application is as a superabsorbent. PAA is used in detergents and dispersantsto the tune of 25%. (Ohara, Takashi *et al.*, 2003)

Disposable diapers contain polyacrylic acid and its derivatives. Acrylic acid is also a key component of Super adsorbent Polymers (SAPs), which are cross-linked polyacrylates capable of absorbing and retaining more than 100 times their own weight in liquid. SAPs havebeen approved for use in packaging with indirect food contact by the US Food and Drug Administration. (Orwoll, Robert A *et al.*, 1999). Detergents frequently contain copolymers of acrylic acid, which aid in dirt sequestration (Ohara, Takashi *et al.*, 2003). Cross-linked polyacrylic acid is also used in the manufacture of household products such as floor cleaners.

PAA has the potential to deactivate the antiseptic chlorhexidine gluconate. (Kaiser, Nancy *et al.*,2009). The neutralized polyacrylic acid gels are biocompatible matrices that can be used in medical applications such as skin care gels. To protect orthopedic implants from corrosion,PAA films can be deposited. Crosslinked AA and gelatin hydrogels have also been used as medical glue.

Paints and cosmetics are two other applications. They stabilise suspended solids in liquids, keep emulsions from separating, and regulate the consistency of cosmetics flow. Carbomer codes (910, 934, 940, 941,

and 934P) indicate molecular weight and specific polymer components. PAAs are used in a variety of applications as alkali metal or ammonium salts, such as sodium polyacrylate (https://en.wikipedia.org/wiki/Polyacrylic_acid#cite_note-8).

Hydrogels derived from PAA have received a lot of attention for their potential use asbandages and wound healing aids. (Mogoşanu, George Dan *et al.*, 2014).

Table No.2 Some pharmaceutical formulations of Carbopol:

Drug	Carrier	Formulation	References
Hydrocortisone	Poly(2-ethyl-2-oxazoline)/ Carbopol	Mucoadhesive Tablets	(46)
Ketoprofen	Anhydrous dicalcium phosphate,talc, and magnesiumstearate, Carbopol 971P solution	Sustained-ReleaseTablets	(47)
Timolol Maleate	Carbopol/ChitosanBased	pH Triggered in Situ Gelling System for Ocular Delivery	(48)
Salbutamol Sulphate	Carbopol 934 /Hydroxyl Propyl Methyl Cellulose	pH Induced In-situ Nasal Gel	(49)
Metronidazole	Sorbitan monostearate- sesame oil organogelcarbopol based	Bigels for topical delivery	(50)
Metformin	Carbopol 934P Chitosan, ethylcellulose, hydroxypropyl methylcellulose	Microspheres	(51)
Pefloxacin Mesylate	0.3% carbopol and 1.5% methylcellulose	In situ gel ophthalmicdrug delivery	(52)
Ketotifen Fumarate	Gellan Gum, SodiumAlginate, Carbomer 934	Ophthalmic drugdelivery system	(53)
Clotrimazole	Coconut oil,pistachio oil, sodiumlauryl sulphate (SLS), Carbopol 934	Gel for topical	(54)
Ciprofloxacin	HPMC, Na CMC, Ethyl cellulose, carbopol 974P	Ocular minitablets	(55)
Sulfacetamide sodium	Hydroxypropyl methylcellulose (HPMCE4M), Carbopol 940/Carbopol 934	pH induced in situ gelsocular dosage forms	(56)
Dyphylline	Carbopol 971 P magnesium stearate, talc	Controlled release tablets	(57)
Lornoxicam	Hydroxypropyl methylcellulose (HPMC) and carbopol, beta- cyclodextrin (β-CD), Tween 80, and oleic acid	Topical Gels Containing Penetration Enhancer	(58)
Etoricoxib	Carbopol 934, HPMC, Stearic acid, Isopropyl Myristate, Tween 80 & Glycerol	Solid lipid nanoparticle (SLN) based topical gel	(59)
Aceclofenac	Chitosan, egg albumin, sodium tripolyphosphate, Sodium tripoly Carbopol 940, cross povidone	Nanoparticles for transdermal delivery	(60)

Recent patents on Carbopol based novel pharmaceutical formulations:
{https://patents.google.com/patent}

Table No.3 Patents published during 2010–2020:

Sr. No	Patent No.	Title of Study	API/Polymer	Application	References
1	US20200237919A1	Diclofenac topical formulation	Diclofenac/ Carbopol	Which can be used topically to treat pain, such as in osteoarthritis.	(61)
2	EP3173067A1	Mucoadhesive buccal in situgel formulation		The current invention is related to *in situ* gelling formulations applied via buccal route,comprising nystatin, a corticosteroid and at least one local anaesthetic.	(62)
3	WO2012176212A1	Carrier based nanogel formulation for skin targeting	Isotretinoin/ Carbopol	This includes various Carbopols, such as Carbopol 934 and Carbopol 980, which can be used as gel formers. Carbopol 934 is a benzene-polymerized cross-linked polyacrylate polymer that is cross-linked with allyl sucrose.	(63)
4	US20200276218A1	Topical pharmaceutical formulations containing a low concentration of benzoyl peroxide in suspension in water and a water-miscible organic solvent	Benzoyl peroxide/ Carbopol	Benzoyl peroxide is commonly used in topical pharmaceutical formulations to treat dermatologic conditions such as acne vulgaris, commonly referred to as acne	(64)
5	US20210205214A1	Novel pharmaceutical formulations	Zolpidem/ Carbopol	The sustained-release polymer isCarbopol.	(65)
6	US20150141389A1	Topical Formulation Compositions Containing Silicone Based Excipients To Deliver Actives To A Substrate	Isododecane/ Carbopol 940	The present disclosure relates to asemi-solid topical drug deliveryformulation including a silicone- based excipient, at least one volatile solvent, at least one active configured to be topically delivered through a patient's skin for an intended therapeutic application, and at least one enhancer	(66)
7	EP3344230A1	Formulations of benzocaine loaded microemulsion based hydrogels for therapeutic purposesand their production method	Benzocaine/ Carbopol	Once these articles were read, it can easily be seen that both gel formulations which are prepared by using either Carbopol or HPMC (hydroxypropyl methylcellulose) extend the duration of the active substance onthe skin's surface.	(67)

8	WO2017212422A1	Topical compositions comprising carbomer forthe treatment and prevention of viral infections and allergic conditions	Oseltamivir/ Carbomer 980	Topically administering to the subject, a composition comprising a therapeutically effective amount of at least one pharmaceutically acceptable carbomer dispersed in an aqueous monovalent salt solution buffered toapproximately neutral pH	(68)
9	CY1119580T1	New Medicinal Preparations Useful InHealth Care	Zolpidem/ Carbopol, sodium carboxy methyl cellulose	Which formulation provides inter alia a measurable plasma drug concentration within 10 minutesof administration.	(69)
10	US10596155B2	Aqueous-based metronidazole gel formulations	Metronidazole/ Carbopol71G Carbopol 971P, Carbopol 974P, Carbopol 980and Carbopol981	The present disclosure relates toaqueous-based gel formulations of metronidazole and their uses, forexample to treat bacterialvaginosis.	(70)
11	US20210244723A1	Formulations and Pharmacokinetiics of Deuterated Benzoquinoline Inhibitors of Vesicular Monoamine Transporter 2	Benzoquinoline Inhibitors/ Carbopol	In certain embodiments, the sustained-release polymeris Carbopol	(71)
12	US11071740B2	Method oftreatment using nanoparticulate ganaxolone formulations	Ganaxolone/ Carbopol	Ganaxolone formulations with improved stability, physical andchemical properties, and enhanced pharmacokinetic properties in mammals, as well as dosage forms containing the same, as well as methods of making ganaxolone formulations and their use in the treatment of epilepsy and other central nervous system disorders	(72)
13	US20100249156A1	Antiviral topical formulations inthe form of abio-adhesive gel	Acyclovir/ Carbopol	It has now been discovered that acyclovir can be advantageously formulated in the form of a hydrophilic gel with ideal viscoelastic and mucoadhesive properties, using vehicles containing hyaluronic acid salts and/or derivatives, in combination with at least one polyacrylic polymer called Carbopol.	(73)
14	AU2019261739B2	Melanin modification compositions and methods ofuse	Melanin/ Carbomer	Compositions may be used for the prevention and treatment of pigmentation disorders, such as post-inflammatory hyperpigmentation and others. The formulations could be used tolighten skin.	(74)
15	US10118981B2	Lactamic polymer containing an acetoacetate moiety	Acetoacetate/ Carbopol	The lactamic polymers may be readily functionalized and the functionalized lactamic polymers may be further derivatized toprovide a wide variety of useful polymers having desirablechemical and physical properties.	(75)

Table No 4: Patents published during 2000–2010

Sr. No	Patent No.	Title of Study	API/Polymer	Application	References
1	US6511660B1	Ophthalmic drug delivery formulations and method for preparing the same	Pilocarpine hydrochloride/Carbopol	The ophthalmic drug delivery formulations are especially suitable for use with ophthalmic drugs such as pilocarpine hydrochloride to treat glaucoma.	(76)
2	US20090069389A1	Novel controlled release- niacin formulation	Niacin/ Carbopol	Since niacin formulations are used for long-term treatment of hyperlipidaemia, the controlled-release niacin formulation of the present invention, capable of maintaining effective blood concentration and high stability for a long period of time, is very useful.	(77)
3	WO2003105804A1	Ibuprofen suspension	Ibuprofen/ Carbomer 934P,Carbopol 974P	The invention provides pharmaceutical agents useful for systemic treatment via the oral route in a form that is easy to administer to children, easy to administer to ageing adults, and easy to administer to adults with motor problems, with improved taste. The invention relates to a stable palatable ibuprofen oral suspension.	(78)
4	US20030044462A1	Sustained release tablets containing bupropion hydrochloride	Bupropion hydrochloride/Carbopol	The effective amount of Carbopol that could be used in the present invention to achieve bupropion hydrochloride stability and sustained release.	(79)
5	CA2673111A1	Ph sensitive matrix formulation	Carbopol 71 G, Hydroxypropyl methylcellulose acetate succinate	The invention's formulations include a therapeutic agent and one or more pH sensitive polymers designed for accelerated hydration, expansion, disintegration, and dissolution at the higher pH of the upper GI tract.	(80)
6	US6420394B1	Topically applied pharmaceutical formulation	NSAID/Carbopol	If a gel formulation is desired, any gel forming agent commonly used in pharmaceutical gel formulations can be used.	(81)
7	US20100273895A1	Formulations of cannabidiol and prodrugs of cannabidiol and methods ofusing the same	Cannabidiol/Carbopol	Pharmaceutical compositions comprising a cannabinoid, such as cannabidiol or a cannabidiol prodrug that is metabolized to cannabidiol, and a penetration enhancer are described herein.	(82)

8	US20030170310A1	Tasteless, directly compressible, fast- dissolving complexes and pharmaceutical formulations thereof	Fexofenadine-Carbomer complex	Processes for preparing, isolating and characterizingthe tasteless complex of the bitter tasting basic drug and processes for producing the pharmaceutical formulations are also disclosed.	(83)
9	JP2010006829A	New composition of minoxidil	Minoxidil/carbomer	The gel compositioncomprises minoxidil (2,4- diamino-6-piperidinylpyrimidin-3-oxide) as a hair-growing effectivecomponent, at least oneorganic or inorganic thickening agent selected fromamong a synthetic polymersuch as a carbomer, a naturally occurring cellulose and its derivative, a non-carbomeric thickening agent	(84)

Table No 5: FDA approved marketed pharmaceutical products derived from Carbopol

Company name	Brand name	FDA approved year and nation	Active pharmaceutical ingredients	Formulation	Investigation application	Route of administration	Ref.
Galderma Laboratories, l. p.	Epiduo	2008	Adapalene and Benzoyl peroxide	Gel	Treat acne	TopicalUse	(85)
AbbVie	Androgel 1.62%	2012	Ethyl alcohol, Isopropyl myristate	Gel	Primary hypogonadism Hypogona dotropic hypogonadism	Topicaluse	(86)
Allergan IndiaPvt.	Pilopine HS	1984	Pilocarpine hydrochloride	Gel	Glaucoma	Ophthalmic	(87)
Entod Pharmaceuticals Ltd.	Timolol	1998	Timololmaleate	Gel	Treat open-angle glaucoma	Ophthalmic	(88)
Alcon, Inc	Nevanac	2005	Nepafenac 0.1%	Eye drop	Treat eye pain	Topical eye drops	(89)
Glenmark Pharmaceuticals Ltd	Acebloc tab	1992.	Carboxymethyl ester of diclofenac	Tablet	Osteoarthritis andRheumatoi d arthritis.	oral	(90)
Allergan plc	Aczone	2005	Dapsone, Diethylene glycol	Gel	Acne Vulgaris	Topicaluse	(91)
Glaxo Smith Kline	Zovirax	2002	Acyclovir	Gel	To treat the Symptoms of herpessimplex virus infections of the skin	Topical Use	(92)
Merck & Co.	Vioxx	2003	Rofecoxib, Sodium alginate	Gel	Rheumatoid arthritisand osteoarthritis	Topicaluse	(93)
Troika Pharmaceuticals Ltd	Procardia	1999	Nifedipine	Gel	Hypertension	Topicaluse	(94)

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