

# Synthesis and Characterization of Novel HPMC Phthalate Succinate Polymers for Pharmaceutical Applications

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## ABSTRACT

**Aim:** The current article aimed to synthesize new HPMC derivative polymers by esterification method. **Background:** 2 most common causes of drug candidate failures are a lack of effectiveness and PK/bioavailability issues. Various strategies have been employed to enhance the aqueous solubility of pharmaceuticals, with one significant technique being solid dispersion. In the last decade, most drug products launched using the solid dispersion technique have utilized HPMCAS polymer as a carrier due to its unique advantages. These products are protected by patents, creating a need for novel polymers to facilitate easier access to generics. **Materials and Methods:** HPMC, Phthalic anhydride, Succinic anhydride, Sodium acetate and Acetic acid were used for the synthesis of new polymer. Polymers with different ratios of phthalate anhydride and succinate anhydride were characterized using various spectroscopic techniques. The effect of the degree of modification on molecular characteristics was examined by FTIR, <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance techniques. Further, novel polymer properties such as glass transition temperature and thermal stability were studied using thermogravimetric analysis and differential scanning calorimetry. The physical form of synthesized polymer was determined using X-ray diffraction analysis technique. For establishing pharmaceutical applications of the novel polymer, solubility and film forming nature were investigated. **Results and Conclusion:** The results confirmed that the synthesis of HPMC derivative is an esterification reaction where -OH in HPMC reacts with anhydride and results in esterification. NMR spectra confirmed successful synthesis of succinate and phthalate succinate derivatives of HPMC. All polymers, except HPMC phthalate succinate 73, displayed an amorphous structure. The novel polymer(s) appears to be rounded to elongated particles with a diameter less than 5 microns and is dense. Compared to the novel polymers synthesized, HPMCAS required more solvent to form a clear solution in the selected solvent system. Polymer films, except HPMC succinate, remained intact in 0.1N HCl (pH 1.2) and acetate buffer (pH 4.5). However, the films were dissolved in phosphate buffer (pH 6.8). The results indicate that the synthesized polymer can be used in enteric coated or gastrointestinal tract targeted drug delivery systems.

**Keywords:** Dissolution enhancement, Hydroxypropyl methylcellulose acetate succinate, Hydroxypropyl methylcellulose phthalate succinate, Polymer synthesis, Solid dispersion.

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## INTRODUCTION

Two most common causes of drug candidate failures are a lack of effectiveness and PK/bioavailability issues.<sup>1</sup> Molecular obesity drives potency during initial drug discovery kills the drug products at later stages because of poor solubility.<sup>2</sup> The overall lipophilicity of the molecules is a primary cause of solubility issues, which in turn affect bioavailability and efficacy. Therefore, even with the use of solubility enhancement methods, achieving

the desired efficacy requires administering a large amount of drug or multiple dosage units.<sup>3</sup> Several strategies have been used to improve the aqueous solubility of pharmaceuticals, including particle size reduction,<sup>4-6</sup> solid dispersion,<sup>7-15</sup> and drug nanoparticles.<sup>16-19</sup>

Cellulose is a highly abundant substance that is obtained from natural sources. The use of this material as fuel may be traced back to ancient times when ancient people relied on it for energy. The origins of modern cellulose chemistry can be traced back to 1837, when Anselme Payen successfully isolated a uniform chemical component from plants. Dumas and a committee of fellow Academicians of Payen named this compound cellulose.<sup>20</sup> Anhydro glucose units were proposed as the building blocks of cellulose as a linear macromolecule in the 1920s. Various



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cellulosic polymer derivatives have been developed and used for different purposes due to their unique properties.

Several polymeric excipients have been approved by the US Pharmacopeia (USP) for use in solid dispersion technology for the manufacturing of amorphous drug products. These include Polyvinylpyrrolidone (PVP), Polyvinylpyrrolidone Vinyl Acetate (PVP-VA), Hydroxypropyl Methylcellulose (HPMC), Hypromellose Phthalate (HPMCP) and Hydroxypropyl Methylcellulose Acetate Succinate (HPMCAS). It is important to mention that most solid dispersions based on HPMCAS polymer are now protected by patents. The industry needs to understand whether solubility enhancement using hydroxypropyl methylcellulose acetate succinate is a myth or reality. There is a demand in the market for alternative polymers because the current polymers are either protected by patents or the polymer like HPMCAS may require higher polymer concentration to convert the crystalline form to amorphous.<sup>3''</sup>

Cellulose is a naturally occurring polysaccharide. It is composed of repeating units of glucose monosaccharides that are joined through  $\beta$  (1-4) glycosidic linkages. The repeating unit consists of hydroxyl groups as the only functional group. Anhydro glucose possesses three hydroxyl groups that exhibit distinct levels of acidity, accessibility for reaction and thus, varying probability for substitution. Chemical modification can change the character of the polysaccharides making them hydrophobic or hydrophilic based on the nature of new group (s) introduced. Each of the three available hydroxyl groups per glucose monomer unit is substituted by methyl- or hydroxypropyl ether or remain unsubstituted in hydroxypropyl methyl cellulose. Methyl and hydroxypropyl groups are attached to the anhydroglucose unit by ether linkage (Methoxy, Hydroxy Propoxy) in HPMC.

HPMCAS is a HPMC derivative, where acetate and succinate groups are attached by ester linkage (acetate, succinate). Acetate groups in HPMCAS are postulated to facilitate hydrophobic drug molecular dispersion. Hydroxyl groups facilitate hydration of resulting solid dispersions in solutions. The presence of ionized carboxylic acid groups derived from succinic acid enhances the *in vivo* stability of colloidal particles. High glass Transition temperatures (T<sub>g</sub>) of the HPMCAS polymer stabilizes amorphous solid dispersion at 40°C and 75% relative humidity. Drug diffusion is the rate-limiting step for crystallization. Below T<sub>g</sub> of spray-dried dispersions, the mobility of the drug is poor and hence inhibits its ability to migrate, phase separation and crystallization.<sup>12</sup>

Considering the above features of HPMCAS, further optimization of the polymer is planned. The aim of the synthesis was to substitute one of the ester functional groups of HPMCAS. The acetyl functional group of HPMCAS planned to substitute with

phthalic group, which is expected to result in a higher T<sub>g</sub> and improved dispersion of hydrophobic drug molecules due to the hydrophobic properties of the phthalic group.

The current study aimed to synthesized HPMC succinate by testing 2 hypotheses: (i) HPMC polymer alone is sufficient for dispersing hydrophobic molecules without the requirement for any specific hydrophobic group and (ii) the succinic acid group is necessary to maintain *in vivo* colloidal stability. Similarly, HPMC phthalate succinate was synthesized using the assumption that the (i) phthalic anhydride is also relatively hydrophobic due to its aromatic structure, which contains a benzene ring in comparison to acetic anhydride used in HPMCAS. The incorporation of a significantly more hydrophobic functional group, such as phthalate, improves hydrophobic molecular dispersion and (ii) succinic acid group is required to stabilize colloidal stability *in vivo*. The process of synthesizing the novel polymer involves an esterification reaction. In this reaction, the Hydroxyl groups (-OH) on HPMC are reacted with a suitable anhydride at 85°C. The synthesized polymers were analyzed using <sup>1</sup>H (<sup>13</sup>C)-NMR, FT-IR and XRD techniques to determine their structures. The thermal examination of the material was performed using Differential Scanning Calorimetry (DSC) and Thermogravimetric Analysis (TGA). The degree of substitution was determined by using <sup>1</sup>H-NMR spectra.

## MATERIALS AND METHODS

### Materials

Hydroxypropyl methylcellulose (METHOCEL E5 Premium LV) was purchased from Colorcon, Goa, India. Succinic anhydride and phthalic anhydride were purchased from Sigma-Aldrich, Darmstadt, Germany. Sodium acetate and acetic acid were purchased from Loba Chemie Pvt. Ltd., Mumbai, India and Thomas Baker, Mumbai, India, respectively.

### Methods

#### Synthesis of HPMC succinate

A 250 mL clean and dry Round Bottom Flask (RBF) equipped with magnetic stirrer and thermometer was charged with 1 g of HPMC E5 and 0.9 g of sodium acetate in 12.5 mL of acetic acid. The flask was rotated at 200 rpm at 85°C until a clear solution was obtained. The RBF was charged with 1.10 g of succinic anhydride and rotated at 200 rpm for 3 hr at 85°C. The reaction mixture was cooled to 25°C and 5.75 mL of deionized water was added to produce a suspension. The reaction mixture was added dropwise into 200 mL of deionized water to produce a gummy solid. Gummy solid was dissolved in 10 mL tetrahydrofuran at 40°C and added dropwise into 100 mL of water. Drying under suction and flushing with nitrogen gas produced a white, gummy solid. Figure 1A presents the scheme for synthesis of HPMC succinate.

## Synthesis of HPMC phthalate succinate

A 1000 mL clean and dry RBF equipped with magnetic stirrer and thermometer was charged with 26 g of HPMC E5, 26 g of sodium acetate in 340 mL of acetic acid. The flask was rotated at 200 rpm at 85°C until a clear solution was obtained. RBF was charged with a suitable quantity of succinic anhydride and phthalic anhydride and rotated at 200 rpm at 85°C for 3 hr to obtain a clear solution (Table 1). After cooling the reaction mixture to 25°C, 50 mL of deionized water was added. The reaction mixture was poured into a larger quantity of deionized water to precipitate. The precipitate was filtered and dissolved in 300 mL of tetrahydrofuran at 40°C. The solution was precipitated by adding excess quantity of water, filtered and the polymer was dried under suction with nitrogen gas flushing. Figure 1B presents the scheme for synthesis of HPMC phthalate succinate.

After the esterification reaction, water was added to the reaction solution to treat unreacted phthalic anhydride and succinic anhydride. Unreacted anhydrides were removed by washing with organic solvent and water repeatedly. During the washing and drying steps, it is thoroughly washed with excess water to remove phthalic and succinic acids.

## Polymer characterization

### Fourier transform infrared analysis

Fourier Transform Infrared (FTIR) study of synthesized compounds was carried out following KBr disk method using a FTIR spectrophotometer (IRTracer-100, Shimadzu). The pellets were prepared by mixing polymer samples and KBr (1:10 ratio), kept in sample holder and scanned from 4000 to 1000  $\text{cm}^{-1}$ .<sup>21</sup>

### <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance analysis

Proton nuclear magnetic resonance (<sup>1</sup>H-NMR) and <sup>13</sup>C NMR analysis of HPMC succinate, HPMC phthalate succinate 41

[phthalic anhydride: succinic anhydride (1:0.25)], HPMC phthalate succinate 73 [phthalic anhydride: succinic anhydride (1:0.43)], HPMC phthalate succinate 32 [phthalic anhydride: succinic anhydride (1:0.66)] analysis of the samples was done using Bruker 500 MHz-Advance III instrument.<sup>22</sup> The number of peaks represented the number of protons present in the compound.<sup>13</sup>C NMR represented the number of C-atoms present in the compound. The samples were prepared by dissolving 1 mg of sample in 0.7 mL of Dimethylsulfoxide (DMSO) and analyzed to obtain <sup>1</sup>H and <sup>13</sup>C NMR spectrums.

### Morphological characterization

Morphological characterization of the powdered sample was done by a Scanning Electron Microscope (SEM) (Inspect F50, EFI company) using a sputter coater (Emiteck K550K, Quorum technology). Powdered samples were spread with a spatula onto a carbon conductive tap on to the sample holder and then coated under platinum in an argon atmosphere using Emiteck K550K sputter coater. Prepared samples were placed under microscope and imaged using a secondary electron detector on field emission gun SEM.<sup>23</sup>

### X-ray diffraction analysis

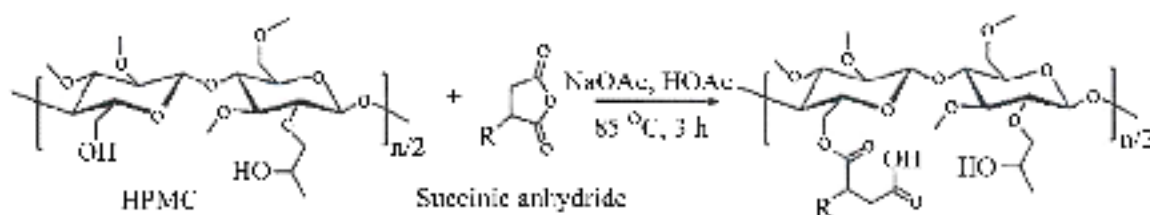
Powdered samples (~50 mg) were packed in a 25 mm specimen ring and analyzed using an X-ray diffractometer (Bruker D8 Advance Diffractometer, Wisconsin, USA) at 22°C. The X-ray source (Cu,  $\lambda=1.5418 \text{ \AA}$ ) was operated at 40 kV voltage and 40 mA current. Samples were scanned from 5 to 40° (2 $\theta$ ) with a step size of 0.02° and a scan rate of 1 s/step.<sup>23</sup>

### Differential scanning calorimetry and Thermogravimetric analysis

Thermal degradation property of HPMC succinate, HPMC phthalate succinate 41 [phthalic anhydride: succinic anhydride (1:0.25)], HPMC phthalate succinate 73 [phthalic anhydride:

**Table 1: Ingredients used for synthesizing HPMC phthalate succinate and corresponding product yield.**

Sample	HPMC E5 (g)	Phthalic anhydride (g)	Succinate anhydride (g)	Yield (g)
HPMC Phthalate Succinate 41	26	35	5.8	28
HPMC Phthalate Succinate 73	26	32	10.0	27
HPMC Phthalate Succinate 32	26	27	12.0	14
HPMC Succinate	26	0	29.0	4



**Figure 1A:** Scheme for the synthesis of HPMC succinate.

succinic anhydride (1:0.43)], HPMC phthalate succinate 32 [phthalic anhydride: succinic anhydride (1:0.66)] samples was analyzed using Thermal Gravimetric Analysis (TGA-50, Shimadzu, Japan). The sample (5 mg) was kept on the crucible under insert conditions and the thermos-grams were obtained between 30 to 300°C.<sup>24</sup>

### Determination of film forming profile and solubility analysis of the polymer

Films were prepared by dissolving individual polymers in dichloromethane and ethanol in a 4:1 ratio. The quantity of polymer was kept constant to understand the quantity of the solvent needed for dissolving the polymer. The film was prepared using a film forming machine (VJTDP-Lab, VJ Instruments, Mumbai, India). The coating head was equipped with manual dragger and coating knife. Before casting, the film casting thickness was manually adjusted at 800  $\mu$ . The cast film was dried at 100°C for 30 min.

## RESULTS

As the molar ratio for succinate in the co-polymer increased (above 40%), the tendency towards gummy nature increased and the isolated yield decreased. This resulted in a low HPMCPS (3:2) yield, as the gummy product was unable to collect in the HPMCPS (0:1), leading to a lower yield.

### Fourier transform infrared analysis

The FTIR spectrum of HPMC showed characteristic peaks at 3550  $\text{cm}^{-1}$  assigned to -OH group stretching, 2900  $\text{cm}^{-1}$  assigned to axial deformation of -C-H bonds in aliphatic chains (-CH<sub>3</sub>) arising from the substitution of hydroxyl groups by methoxy and hydroxypropyl, 1650  $\text{cm}^{-1}$  assigned to axial deformation of carbonyl group in glucose and 1300-900  $\text{cm}^{-1}$  assigned to axial deformation of C-O-C bonds of cellulose ethers. The FTIR spectrum of HPMC succinate showed a characteristic broad peak at 3550  $\text{cm}^{-1}$  assigned to -OH group stretching (intensity reduced because of esterification), 2900  $\text{cm}^{-1}$  assigned to axial deformation of -C-H bonds in aliphatic chains (-CH<sub>3</sub>) arising from substitution of hydroxyl groups by methoxyl and hydroxypropyl, 1765  $\text{cm}^{-1}$  assigned to -C=O stretch of ester (this peak is absent in HPMC) and at 1650  $\text{cm}^{-1}$  assigned to axial deformation of carbonyl group in glucose and peak at 1300-1000  $\text{cm}^{-1}$  assigned to -C-O stretch (change can be clearly seen with respect to HPMC) (Figure 2). FTIR spectrum of HPMC phthalate succinate showed a characteristic broad peak at 3550  $\text{cm}^{-1}$  assigned to -OH group stretching (intensity reduced because of esterification), 2900  $\text{cm}^{-1}$  assigned to axial deformation of -C-H bonds in aliphatic chains (-CH<sub>3</sub>) arising from substitution of hydroxyl groups by methoxyl and hydroxypropyl, 1765  $\text{cm}^{-1}$  -C=O stretch of ester (this is absent in HPMC), 1650  $\text{cm}^{-1}$  assigned to axial deformation of carbonyl group in glucose and 1300-1000  $\text{cm}^{-1}$  assigned to -C-O stretch (change can be clearly seen with respect to HPMC).

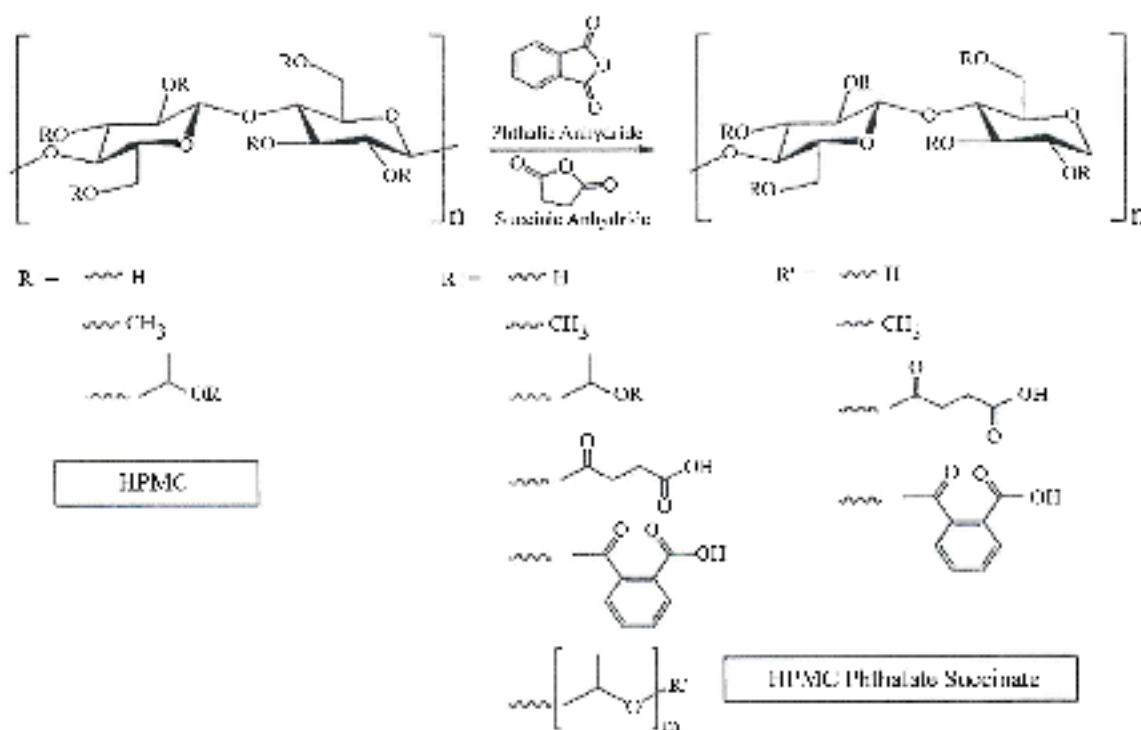


Figure 1B: Scheme for the synthesis of HPMC phthalate succinate.

### <sup>1</sup>H and <sup>13</sup>C nuclear magnetic resonance analysis

Chemical shift values of the <sup>1</sup>H (<sup>13</sup>C)-NMR spectra of Synthesized polymer (s) were recorded in DMSO solvent medium. <sup>1</sup>H-NMR spectrum of HPMC succinate demonstrated 0.5 protons at 1.7 to 2.1 ppm related to HPMC succinate (Figure 3A). <sup>13</sup>C-NMR spectrum showed 2 peaks in the region of 160-220 ppm detected that are related to carbonyl carbons of the succinate functional group (Figure 3B).

The <sup>1</sup>H-NMR spectrum of HPMC phthalate succinate 41 [phthalic anhydride: succinic anhydride (1:0.25)] exhibits a variety of frequencies (Figure 3C). The analysis revealed the presence of 3.38 protons in the range of 1.7 to 2.1 ppm, which are associated with succinate. Additionally, 4 protons were detected in the range of 7.50 to 8.01 ppm, which are related to phthalate. Furthermore, 1 proton was observed at 13 ppm, also associated with phthalate. The data indicates that the ratio of phthalate to succinate is 1:0.35 (1.3892/4=0.3473). The results closely approximate the reaction ratios. The <sup>13</sup>C-NMR spectrum of HPMC phthalate succinate 41, with a ratio of Phthalic anhydride to Succinic anhydride of 1:0.25, exhibited three peaks in the 160-220 ppm range, which corresponded to the carbonyl carbons of the succinate and phthalate functional groups. Additionally, three peaks in the 140-120 ppm range were observed, indicating the presence of aromatic carbon in the phthalate group (Figure 3D).

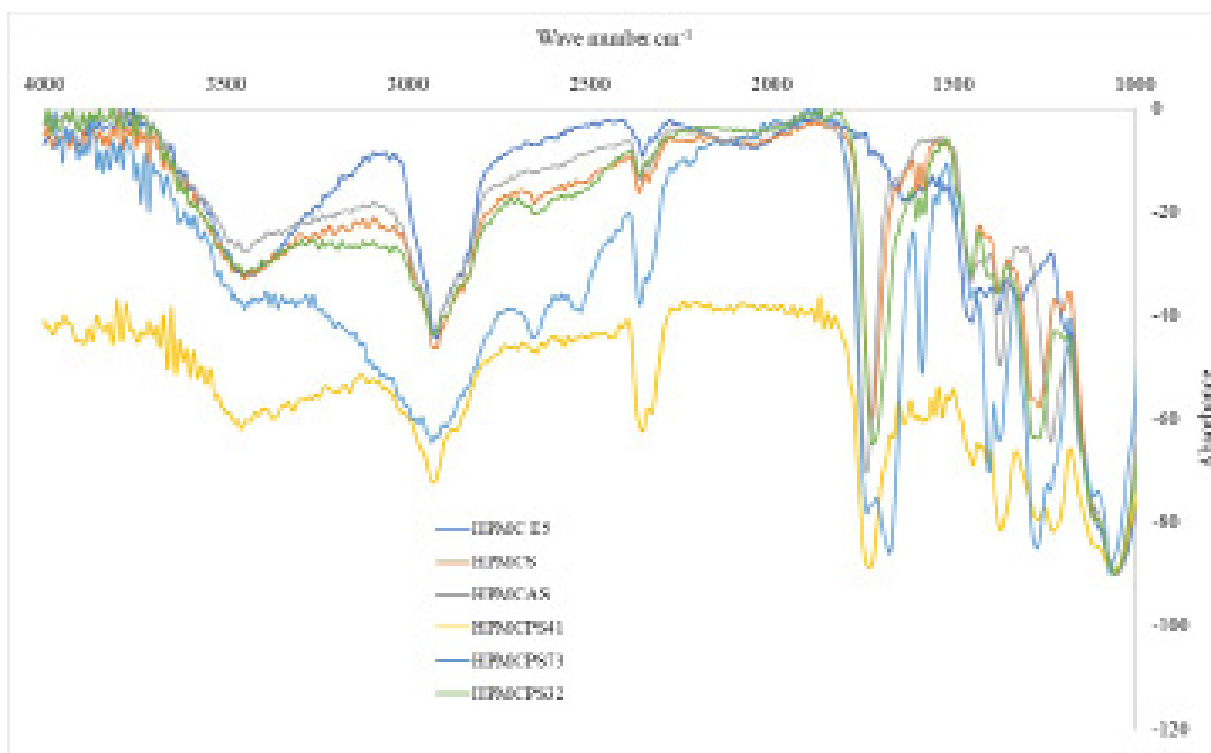
The <sup>1</sup>H-NMR analysis of HPMC phthalate succinate 73, which was synthesized using a ratio of phthalic anhydride to succinic anhydride of 1:0.43, revealed the presence of 3 protons in the

chemical shift range of 1.7 to 2.1 ppm, which are associated with succinate. Additionally, 4 protons were seen in the chemical shift range of 7.50 to 8.01 ppm, which are attributed to phthalate. Furthermore, a single proton was detected at a chemical shift of 13 ppm, also related to phthalate. The ratio between phthalate and succinate is 1:0.75 (3.0036/4=0.7509) (Figure 3E). The <sup>13</sup>C-NMR of HPMC phthalate succinate 73 was obtained using a mixture of phthalic anhydride and Succinic anhydride at a ratio of 1:0.43. Three peaks were observed in the 160-220 ppm range, which were attributed to the presence of carbonyl carbons in succinate and phthalate functional groups. Additionally, three peaks were discovered in the 140-120 ppm range, which were associated with aromatic carbon atoms in the phthalate group (Figure 3F).

The <sup>1</sup>H-NMR analysis of HPMC phthalate succinate 32 [phthalic anhydride: succinic anhydride (1:0.66)] revealed the presence of 0.5 protons, attributed to succinate, in the chemical shift range of 1.7 to 2.1 ppm. Additionally, 4 protons were observed in the chemical shift range of 7.50 to 8.01 ppm, indicating the presence of phthalate. Furthermore, a single proton was detected at a chemical shift of 13 ppm, also associated with phthalate. The

**Table 2: Results of glass transition temperatures.**

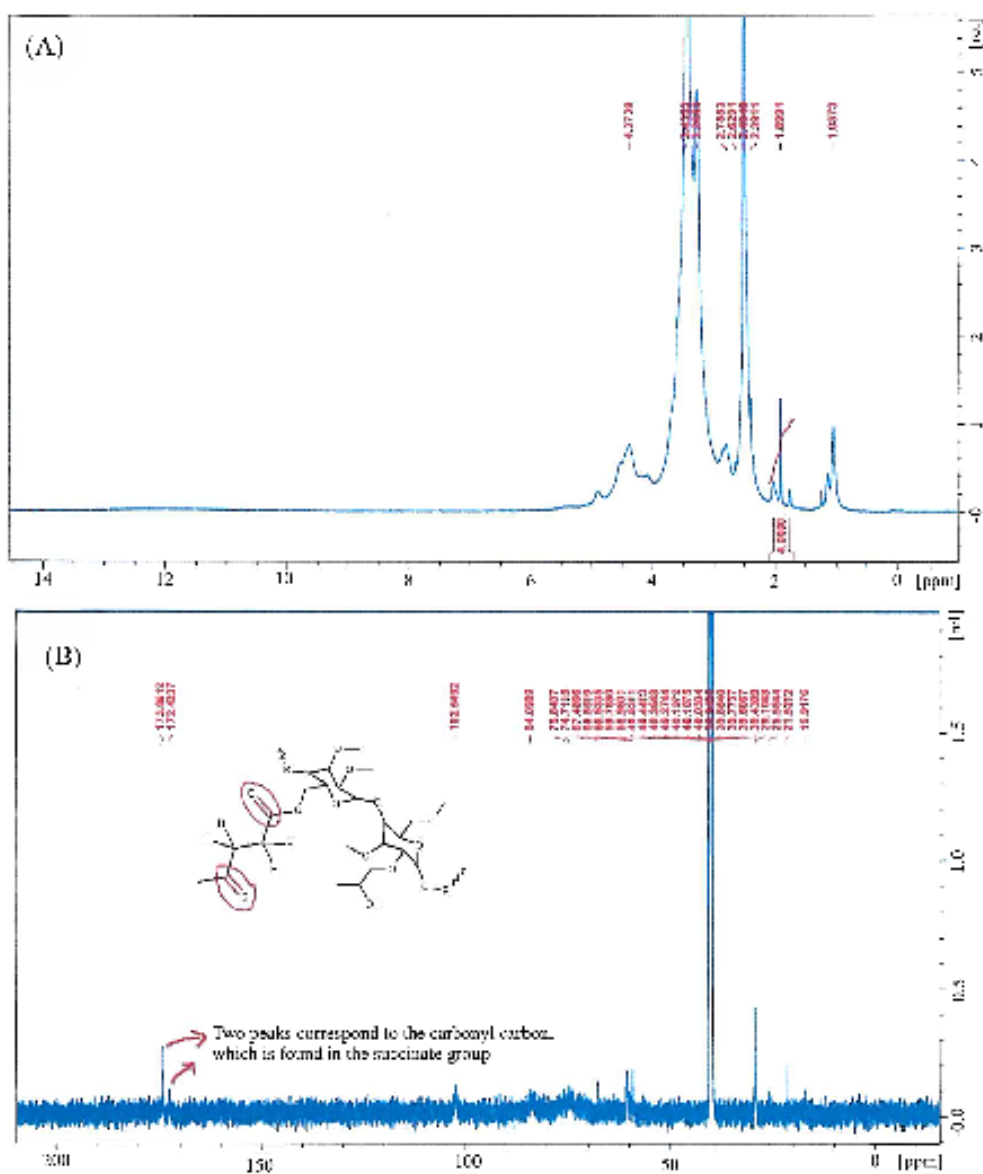
Polymer	Tg (°C)
HPMC	178.9
HPMC phthalate succinate 41	--
HPMC phthalate succinate 73	138.4
HPMC phthalate succinate 32	156.8



**Figure 2:** FTIR spectra of HPMC, HPMC succinate, HPMC phthalate succinate 41, HPMC phthalate succinate 73 and HPMC phthalate succinate 32.

**Table 3: Film forming nature and solubility of the polymer at different pH conditions.**

Polymer	Amount of polymer (g)	DCM (mL)	Ethanol (mL)	Remarks
HPMCAS	0.5	41.4	10.35	Required excess solvent to dissolve and formed a continuous film.
HPMC succinate	0.5	13.8	3.45	Formed a good film.
HPMC phthalate succinate 41	0.5	13.8	3.45	Formed a poor film, the film was not continuous.
HPMC phthalate succinate 32	0.5	13.8	3.45	Formed a very good continuous film.
HPMC phthalate succinate 73	0.5	13.8	3.45	Solution was not clear, little hazy and formed a good film.

**Figure 3 A-B:** <sup>1</sup>H-NMR spectrum (A) and <sup>13</sup>C-NMR spectrum (B) of HPMC succinate.





occurs in 2 stages. The experiment stopped at 300°C, considering the obvious third stage of mass loss because of excess carbon and ash residues.

### Film forming nature and solubility of the polymer

HPMCAS required more solvent to form a clear solution in the selected solvent system in comparison with the novel polymers synthesized (Table 3).

### Solubility analysis of the polymer film

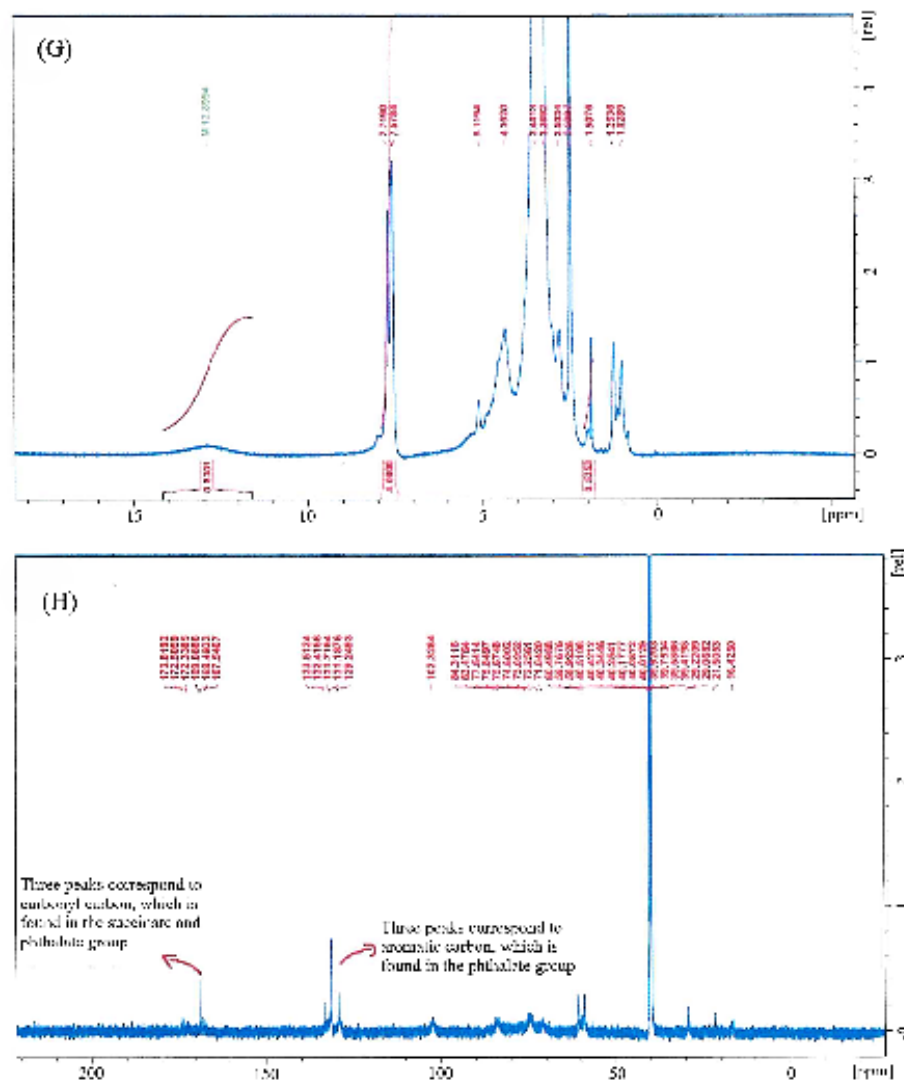
Buffer solutions were prepared following the guidelines outlined in the United States Pharmacopeia-National Formulary (USP-NF). The solubility of prepared polymer films was evaluated at different pH conditions (0.1 N HCl, pH 4.5 acetate buffer and pH 6.8 phosphate buffer). Results of solubility study of polymer film showed that none of the polymers dissolved in 0.1 N HCl (pH 1.2). HPMC succinate partially dissolved in acetate buffer (pH

4.5). HPMCAS, HPMC succinate and HPMC phthalate succinate 41 were immediately dissolved in phosphate buffer (pH 6.8). However, HPMC phthalate succinate 32 and HPMC phthalate succinate 73 did not easily dissolved in phosphate buffer (pH 6.8). Results of solubility analysis of HPMCAS, HPMC succinate, HPMC phthalate succinate 41, HPMC phthalate succinate 32 and HPMC phthalate succinate 73 are shown in Table 4.

## DISCUSSION

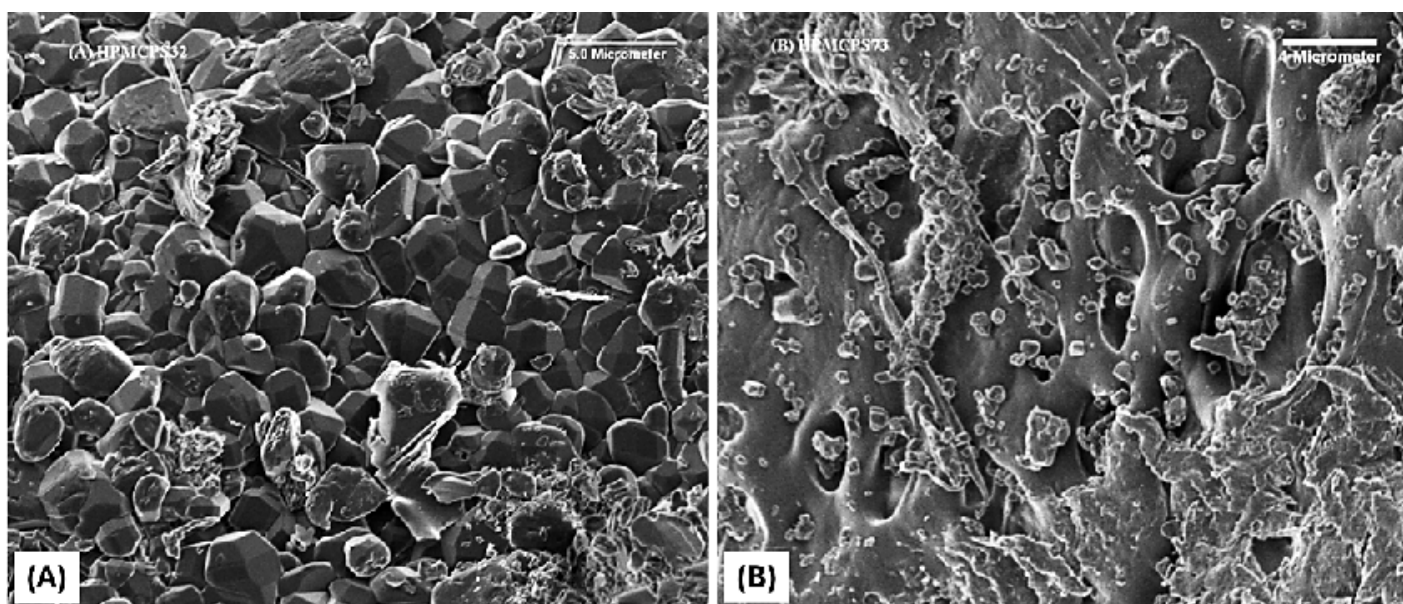
The FT-IR spectra of synthesized novel polymers agree with the literature reports for functional groups. The results confirmed that the synthesis of HPMC derivative is an esterification reaction where -OH in HPMC reacts with anhydride and results in esterification.

The <sup>1</sup>H-NMR analysis of HPMC phthalate succinate polymers revealed additional protons that are related to succinate and

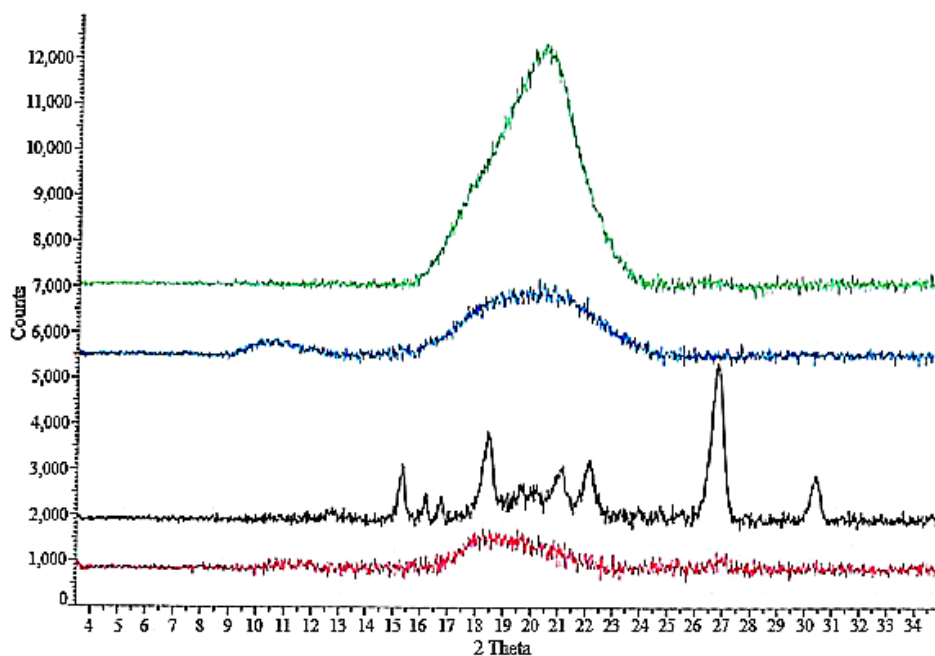


**Figure 3 G-H:** <sup>1</sup>H-NMR spectrum (G) and (H) <sup>13</sup>C-NMR spectrum of HPMC phthalate succinate 32

[phthalic anhydride: succinic anhydride (1:0.66)].



**Figure 4A-B:** SEM images of HPMC phthalate succinate 32 (A) and HPMC phthalate succinate 73 (B).



**Figure 4C:** X-ray diffraction spectrum of HPMC succinate (Red), HPMC phthalate succinate 73 (Black), HPMC phthalate succinate 41 (Blue), and HPMC phthalate succinate 32 (Green).

phthalate. The practically observed phthalate succinate ratios (1:0.35, 1:0.75, 1:0.13) in the synthesized polymers were different compared to the theoretical experimental reaction ratios [41 (1:0.25), 73 (1:0.43), 32 (1:0.66)] respectively. The  $^{13}\text{C}$ -NMR spectrum of HPMC phthalate succinate polymers [41 (1:0.25), 73 (1:0.43), 32 (1:0.66)] revealed additional carbonyl carbons of the succinate and phthalate functional groups and aromatic carbon in the phthalate group. Morphological characterization using PXRD and SEM revealed that the newly synthesized polymers are in amorphous nature with particles size  $< 5 \mu$ . During Thermal Analysis (DSC/TGA), weight losses occur in 2 stages. The solvent

(tetrahydrofuran) is responsible for a maximum initial loss of 3% within the temperature range of 30°-80°C. The newly synthesized polymers exhibit stability within the temperature range of 80°C to 160°C. During the second stage, thermal degradation takes place at temperatures ranging from around 160°C to 280°C, resulting in an average reduction of around 50%. This stage may be attributed to the oxidative degradation of cellulose ethers, which involves intramolecular dehydration and demethylation process. The glass transition temperature of HPMC phthalate succinate 32 is greater than HPMC phthalate succinate 73. HPMC succinate glass transition temperature appears to be very low, exact

number could not determine. However, increase in succinate concentration in the polymer increases the gummy nature. This is also reflected in the decrease in the yield of the polymer. The yield of the polymer is as follows: HPMC phthalate succinate 41 (0.25)>HPMC phthalate succinate 73 (0.43)>HPMC phthalate succinate 32 (0.66)>HPMC succinate. During solubility analysis, the amount of solvent required to form a clear solution for novel polymers observed is significantly less compared to HPMCAS, highlighting their eco-friendly nature. Additionally, these novel polymers exhibit excellent film forming properties. The film forming nature of the synthesized polymers can be graded as follows HPMC phthalate succinate 32>HPMC phthalate succinate 73>HPMC succinate>HPMC phthalate succinate 41. Solubility analysis of the polymer films revealed that the rate of solubility of the polymers can be qualitatively graded as follows: HPMC succinate>HPMC phthalate succinate 41>HPMC phthalate succinate 32>HPMC phthalate succinate 73. Polymer films remained intact in 0.1N HCl (pH 1.2) and except HPMC succinate others remained intact in acetate buffer (pH 4.5). However, the films were dissolved in phosphate buffer (pH 6.8). This indicates that the synthesized polymer can be used in enteric coated or gastrointestinal tract targeted drug delivery systems.

## CONCLUSION

HPMC ester polymers have been synthesized as an alternative to HPMCAS polymer and are characterized by FTIR and NMR spectroscopy. The glass transition temperature has been determined by DSC. Based on solubility and film forming analysis of the newly synthesized polymers, we anticipate a wide range of pharmaceutical applications namely as film formers, in the preparation of pH dependent drug delivery systems and solid dispersions.

## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

## ABBREVIATIONS

**HPMC:** Hydroxypropyl methylcellulose; **HPMCAS:** Hydroxypropyl methylcellulose acetate succinate; **FTIR:** Fourier transform infrared spectroscopy; **NMR:** Nuclear magnetic resonance; **SEM:** Scanning electron microscope; **DSC:** Differential scanning calorimetry; **TGA:** Thermogravimetric analysis.

## SUMMARY

Pharmacokinetics (PK) and bioavailability are crucial in drug discovery and development. The most common causes of drug failures are lack of effectiveness and PK/bioavailability issues. Numerous strategies have been utilized to improve the aqueous solubility of pharmaceuticals, with solid dispersion being a particularly effective technique.

In the last decade, most drug products launched using the solid dispersion technique have utilized HPMCAS polymer as a carrier due to its unique advantage of maintaining drugs in a supersaturated state, significantly enhancing their solubility and bioavailability. These products are protected by patents, creating a need for novel polymers to facilitate easier access to generics.

The current research aimed to synthesize new HPMC derivative polymers by replacing the acetate group in HPMCAS by Phthalate group using esterification method. HPMC, phthalate anhydride and succinate anhydride were used for the synthesis of new polymer. Polymers with different ratios of phthalate anhydride and succinate anhydride were characterized using various spectroscopic techniques.

The results confirmed that the synthesis of HPMC derivative is an esterification reaction where -OH in HPMC reacts with anhydride and results in esterification. NMR spectra confirmed successful synthesis of succinate and phthalate succinate derivatives of HPMC. The <sup>1</sup>H-NMR analysis of HPMC phthalate succinate polymers revealed additional protons that are related to succinate and phthalate. The practically observed phthalate succinate ratios (1:0.35, 1:0.75, 1:0.13) in the synthesized polymers were different compared to the theoretical experimental reaction ratios [41 (1:0.25), 73 (1:0.43), 32 (1:0.66)] respectively. The <sup>13</sup>C-NMR spectrum of HPMC phthalate succinate polymers [41 (1:0.25), 73 (1:0.43), 32 (1:0.66)] revealed additional carbonyl carbons of the succinate and phthalate functional groups and aromatic carbon in the phthalate group. All polymers, except HPMC phthalate succinate 73, displayed an amorphous structure. The novel polymer (s) appear to be rounded to elongated particles with a diameter less than 5 microns and are fairly dense. Compared to the novel polymers synthesized, HPMCAS required more solvent to form a clear solution in the selected solvent system. Polymer films remained intact in 0.1N HCl (pH 1.2) and except HPMC succinate others remained intact in acetate buffer (pH 4.5). However, the films were dissolved in phosphate buffer (pH 6.8). The results indicate that the synthesized polymer can be used in enteric coated or gastrointestinal tract targeted drug delivery systems. Based on the solubility properties, the newly synthesized polymer(s) have potential to be explored in the solid dispersion technique.

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