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# Synthesis and Evaluation of 2-Hydroxymethylene Cross-Linked Dextrins as Tablet Superdisintegrants

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**Abstract :** Disintegrants are the essential components of a tablet. Cross-linking of dextrin with epichlorohydrin induces hydrophobization in hydrophilic dextrin to give 2-hydroxymethylene cross-linked dextrin (HMCD). This in turn gives good swelling power in water. Dextrin is cross-linked with different percentage of epichlorohydrin by weight. Cross-linking is done from 5-50% of epichlorohydrin to dextrin. The crosslinking of 20% epichlorohydrin with dextrin is known as HMCD-20 exhibited best swelling. It was characterized by IR, MALDI spectroscopy and DSC studies. To evaluate the disintegrant property of HMCD-20, paracetamol tablets were prepared by wet granulation method and folic acid tablets by direct compression technique. A comparison study was also done using disintegrating agents such as cornstarch and superdisintegrants sodium starch glycolate, croscarmellose sodium, and crospovidone. HMCD-20 exhibited better disintegrating property in wet granulation method (< 1 min) in comparison with direct compression method (<4 min). HMCD-20 was found to be safe up to 2000 mg/kg in mice.

**Key words:** Superdisintegrant, 2-Hydroxymethylene cross-linked dextrin, Swelling capacity, Degree of cross-linking, Flow Properties, Disintegration time.

## Introduction

Disintegration is an important factor affecting drug release, absorption into the systemic circulation, and subsequent pharmacological effects. The proper choice of disintegrant and its consistency of performance are critical to the formulation development of tablets. The term disintegrant is used to refer to a substance that is added to a tablet formula for causing the compressed tablet to break apart when placed in an aqueous environment [1]. A disintegrant is normally added to facilitate the rupture of bonds and subsequent disintegration of the tablets. This increases the surface area of the drug exposed to the gastrointestinal fluid; incomplete disintegration can result in incomplete absorption or a delay in the onset of action of the drug. There are several types of disintegrants, acting with different mechanisms [2]: (a) promotion of the uptake of aqueous liquids by capillary forces, (b) swelling in contact with water, (c) release of gases when in contact with water and (d) destruction of the binder by enzymatic action. Traditional tablet disintegrants such as starches (e.g. corn, wheat, potato, rice and pregelatinized starch), macromolecules (e.g. alginic acid, sodium alginate, polacrilin potassium, and guar gum), finely divided solids (e.g. colloidal silicon dioxide and magnesium aluminum silicate), and

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celluloses (e.g. powdered cellulose, microcrystalline cellulose, carboxymethylcellulose, methylcellulose, and low-substituted hydroxypropylcellulose) are used in 5-20% w/w of tablet, and typically exhibit disintegration time about 10-30 min at the hardness of 6-8 kg [3].

In more recent years, increasing attention has been paid to formulate not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth [4]. The simplest way to achieve quick disintegration is to use a superdisintegrant in concert with suitable diluents. Superdisintegrants are used in 1-10% w/w of the tablet [5] and exhibit disintegration time of 1-5 min. In some cases, even less than 1 min. Superdisintegrants are effective at low concentration, have greater disintegrating efficiency and are more effective intragranularly. These superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leads to an enormous increase in the volume of granules to promote disintegration [6]. Superdisintegrants such as croscarmellose sodium, crospovidone and sodium starch glycolate are frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thereby increase the rate of drug dissolution [7, 8,9,10]. However, these superdisintegrants are plagued by certain disadvantages such as, very high swelling (up to 300 times), ionic nature, high amount of inorganic impurities, up to 10% sodium chloride in case of sodium starch glycolate; high amount of water and sodium chloride (0.5%), non-native to human in case of croscarmellose; high nitrogen content (14%), hygroscopisity, and incompatibilities with certain drugs in case of crospovidone. The above disadvantages and limited choice of superdisintegrants gives formulation development scientist a little choice to play around with superdisintegrants. Hence there is need for novel superdisintegrants.

Dextrin is a polymeric carbohydrate, which is formed during the hydrolysis of starch to sugars by heat, by acids, and by enzymes. Dextrin and starch have the general formula, $[C_x H_2O)_y)]_n$- (y = x - 1), in which glucose units are connected to one another usually head-to-tail, but dextrin has a smaller and less complex molecule than starch. Dextrin is water-soluble and water solubility dextrin varies from the starch source and the way starch is processed [11]. Dextrin is abundantly available commercially at the price similar to starches. Dextrin cross-linked with various cross linking agents are used for cation exchangers [12], iodophores [13] etc. However to our knowledge, there is no description of 2-hydroxymethylene cross-linked dextrin as tablet excipient and particularly as tablet disintegrant in the literature.

The present paper describes synthesis of 2-hydroxymethylene cross-linked dextrins obtained by cross-linking dextrin with various concentrations of epichlorohydrin (5-50%) by weight and detailed evaluation of dextrin cross linked with 20% epichlorohydrin (HMCD-20) for tablet disintegrating effect.

## Materials and Methods

### Materials

The key raw material yellow dextrin was commercial of grade (Kalandikars, Ahmedabad, India), other chemicals : epichlorohydrin (Sd fine chemicals ltd) and span 80 (CDH) are of laboratory grade. The other formulation ingredients paracetamol, folic acid, (Sri Krishna drugs limited), Avicel PH 101 (FMC Biopolymer), Avicel PH 102 (FMC Biopolymer), DCL 21 (Fonterra excipients), dicalcium phosphate (Rhodia UK ltd), corn starch (FMC Biopolymer), sodium starch glycolate (Roquette), croscarmellose (FMC Biopolymer), crospovidone (ISP Technologies), magnesium stearate (Ferro industries Quimicas LDA) are from the qualified vendors of Natco Pharma ltd.

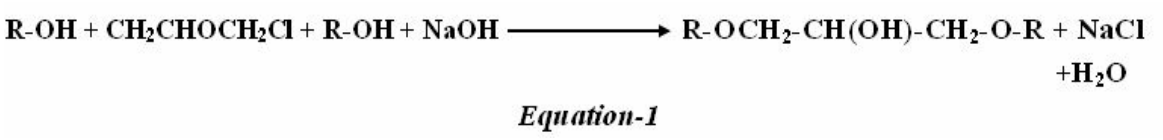
### Synthesis of 2-Hydroxymethylene Cross-linked Dextrins (HMCD) [14, 15]

### Synthesis of 2-Hydroxymethylene Cross-linked Dextrin (HMCD-20)

To a solution of 3.1 N sodium hydroxide in water (50 ml), dextrin (50 g), sodium borohydride (0.75 g), toluene (125 ml), span 80 (3.75 g), epichlorohydrin (10g) were added and stirred at $70^0$C for about 5h. Initially the reaction mixture was homogenous solution. As the cross-linking takes place, the reaction mixture turns into suspension. After heating for 5h the reaction mixture was cooled to room temperature, followed by addition of water and adjustment of pH to 6.5 using 2N hydrochloric acid. The precipitated product was initially washed with water and then with acetone. The product was dried at $45^0$C under vacuum for 6-8h. (Equation-1).

Similarly, 5-50% 2-hydroxymethylene cross-linked dextrins were synthesized by taking 2.5-25% epichlorohydrin. 5-15% 2-hydroxymethylene cross-linked dextrins could not be isolated by precipitation from water, as these were soluble in water and hence were isolated by lyophilization of reaction mixture.

The percentage of dextrin, epichlorohydrin and the percentage yield of 2-hydroxymethylene cross-linked dextrin along with the physical properties of various 2-hydroxymethylene cross-linked dextrins are shown in the table-1.




*Equation-1*

**Table 1: Physical properties of various 2-hydroxymethylene cross-linked dextrins**

| % of Epichlorohydrin | % of Dextrin | % Yield of HMCD | Properties | |
|---|---|---|---|---|
| | | | Appearance | Water solubility |
| 5 | 95 | 29.4 | Whitish flakes | Water soluble |
| 10 | 90 | 40.3 | Whitish Powder | Water Soluble |
| 15 | 85 | 56.5 | Yellow jelly mass | Partially Water soluble |
| 20 | 80 | 79.4 | Yellowish powder | Water Insoluble |
| 25 | 75 | 92.4 | Yellowish powder | Water Insoluble |
| 30 | 70 | 88.3 | Yellowish powder | Water Insoluble |
| 35 | 65 | 93.7 | Yellowish powder | Water Insoluble |
| 40 | 60 | 84.8 | Yellowish powder | Water Insoluble |
| 45 | 55 | 91.3 | Yellowish powder | Water Insoluble |
| 50 | 50 | 89.8 | Yellowish powder | Water Insoluble |

**Characterization of HMCD**

**Fourier transform infrared spectroscopy (FTIR)**

FTIR spectra were recorded on samples (Dextrin & HMCD) prepared in potassium bromide (KBr) disks using a Perkin Elmer FTIR. Samples were prepared in KBr disks in a hydrostatic press at 6-8 tons pressure. The scanning range was 500 to 4000 $cm^{-1}$.

**Differential Scanning Calorimetry (DSC)**

The thermal properties of (Dextrin & HMCD) were characterized by using a differential scanning calorimeter (Mettler Toledo DSC 821e). The Samples were first heated from 40 °C to 350°C under nitrogen atmosphere at a heating rate of 10 °C/min.

**Maxtrix-assisted Laser Desorption Ionization-Time of Flight Mass Spectroscopy**

The molecular weights of dextrin and 2-hydroxymethylene cross-linked dextrin were measured using Applied Biosystems (Voyanger-DE) matrix-assisted laser desorption ionization-time of flight (MALDI-TOF) mass spectrometer system.

**Swelling capacity of HMCD**

**Determination of Swelling Capacity**

One gram of 2-hydroxymethylene cross-linked dextrins were added into a stoppered 50 ml measuring cylinder containing 40 ml water, shaken gently three times for 30 seconds and was allowed to stand for 240 minutes after making up the volume to 50ml with water. Volume occupied by 2-hydroxymethylene cross-linked dextrins was noted at 15, 30, 60 and 240 minutes. The volume occupied by disintegrating agent including adhering mucilage was measured. The test was carried out in triplicate and the average value of swelling index was recorded.

**Acute toxicity study**

Swiss albino mice weighing 25-30gm were purchased from Mahavir Agencies Ltd. (Hyderabad, India). All the procedures were conducted in compliance with guidelines established by the National Institutes of Laboratory Animal Welfare. The study has the approval from Institutional Animal Ethical Committee. Animals were acclimatized in temperature (22°C ± 2°C) and humidity (60 ± 10%) controlled rooms with 12 hrs light/dark cycle for at least 1 week before the experiment. Regular laboratory chow and tap water were allowed ad libitum. Nutrient animal feed was obtained from Rayon Biotech ltd.

The animals were divided into two groups of six each. The treatment group received HMCD-20 suspended in normal saline orally at a dose of 100, 500, 1000, 2000 mg/kg body weight. Control group were treated with an identical volume of normal saline. The animals were observed for behavioral changes during the first 4 hrs and mortality if any for 72 hrs.

**Preparation of tablets by wet granulation method**

The drug substance (paracetamol) was combined with dicalcium phosphate (diluent), various concentrations of different disintegrants (HMCD-20, corn starch, sodium starch glycolate, croscarmellose sodium, and crospovidone) and processed with the use of slurry

containing a binder (starch paste) with subsequent drying and milling to produce granules. The resulting granules were then blended with additional excipients (Mg stearate & disintegrant added extragranularly) and compressed into tablets at two different compressional forces to give tablets with hardness of 6-8 kg and 8-10 kg. The tablets were compressed using a 12 stationed Rimek Mini Press using size D, 9mm flat-faced beveled edge tooling.
The tablets were evaluated for disintegration time according to USP protocol. The composition of 250 mg tablet is shown in table 2a and disintegration data are shown in table 2b.

For comparison purpose tablets were also made using marketed disintegrants corn starch, sodium starch glycolate, crosscarmellose, crospovidone.

**Preparation of tablets by direct compression method**

Folic acid (drug), dicalcium phosphate (diluent), various concentrations of different disintegrants (HMCD-20, corn starch, sodium starch glycolate, croscarmellose sodium, crospovidone), starch paste (binder) were blended together for 5 minutes. Then magnesium stearate was added and blended for an additional 2 minutes. The tablets were compressed using a 12 stationed Rimek Mini Press using size D, 9mm flat-faced beveled edge tooling at two different compressional forces to give tablets with hardness of 6-8 kg and 8-10 kg. The target tablet weight was 250mg.
The tablets were evaluated for disintegration time according to USP protocol. The composition of a typical 250 mg tablet is shown in table 3a and disintegration data are shown in table 3b.

**Evaluation of powder blend and granules**

**Bulk and tapped density**

Bulk and tapped densities were determined by a modification of the method of Kumer and Kothari. The powder was placed inside the measuring cylinder of a tapped density apparatus and the bulk volume, V1, was recorded and subjected to 750 taps and the tapped volume, V2, was recorded. The bulk and tapped densities were computed as
Bulk density = weight of powder/V1 …… (I)
Tapped density = weight of powder/V2……. (II)

**Powder flow properties**

Free flowing powder properties were measured by Compressibility Index and Hausner's ratio. Compressibility Index was calculated by using the formula,
Compressibility Index = $(\rho_t-\rho_b / \rho_t)$ 100, Hausner's ratio HR= $( \rho_t / \rho_b )$ .
$\rho_t$ = Tapped density, $\rho_b$= Initial bulk density.

## Evaluation of tablets

**Friability**

Friability was determined using an Electrotab friabilator. Twenty four tablets (6gm) per batch were weighed and caused to cascade in the drum of the friabilator which rotated at 100 rpm dropping the tablets at a height of 6 inches for each revolution. The tablets were dusted and reweighed. The loss in weight caused by fracture or abrasion was expressed as a percentage of the original weight of twenty four tablets, calculated as the friability of the tablets. Determinations were made in triplicate and the mean values were used.

**Tablet hardness**

The crushing strength of each of 3 tablets was determined using a Monsanto tablet Hardness tester. The results were reported as the mean of 3 individual measurements.

**Tablet weight uniformity**

Twenty tablets were selected at random and average weight was determined. Then individual tablets were weighed and compared with average weight.

**Disintegration of tablets**

Disintegrating time was measured in distilled water at $37\pm1^0$C, pH 6.5, according to the method described by the US Pharmacopoeia USP XXIII, using a tablet disintegration tester apparatus (Electrolab disintegrating tester USP). The tablets were considered completely disintegrated when all particles passed through the wire mesh; tablets with a surface erosion disintegration pattern retained their size with time. Ten measurements were taken for each tablet formulation. Mean values and standard deviations were calculated.

**Table 2a** : **Tablet Formulation by Wet Granulation Method**

| Drug (%) | Binder (%) | Diluent (%) | Lubricant (%) | Disintegrant[a] (%) | | | |
|---|---|---|---|---|---|---|---|
| Paracetamol (2) | Avicel PH102 (26.5-19) Starch Paste(10) | DCP 21 (10) | Magnesium Stearate(1) | 2.5 | 5 | 7.5 | 10 |

[a]The disintegrant - corn starch or sodium starch glycolate or croscarmellose sodium or crospovidone or HMCD-20, DCP - Dicalcium Phosphate.

**Table 2b: Disintegration Test Results of Tablets Prepared by Wet Granulation Method**

| | Disintegrant (%) | Disintegration time (in min) | | | | |
|---|---|---|---|---|---|---|
| | | HMCD-20 | Corn starch | Sodium Starch Glycolate | Cros-carmellose | Crospovidone |
| Hardness 6-8 Kg | 2.5 | 0.56 ± 0.30 | 8.14 ± 0.44 | 0.33 ± 0.06 | 3.00 ± 0.30 | 1.22 ± 0.11 |
| | 5 | 0.53 ± 0.24 | 1.46 ± 0.06 | 1.18 ± 0.05 | 1.12 ± 0.08 | 1.03 ± 0.27 |
| | 7.5 | 0.45 ± 0.07 | 1.66 ± 0.22 | 2.27 ± 0.29 | 2.37 ± 0.09 | 3.43 ± 0.07 |
| | 10 | 0.42 ± 0.01 | 1.40 ± 0.13 | 0.37 ± 0.05 | 3.20 ± 0.1 | 0.33 ± 0.04 |
| Hardness 8-10 Kg | 2.5 | 3.31 ± 0.10 | 11.99 ± 0.4 | 1.16 ± 0.23 | 5.17 ± 0.10 | 5.24 ± 0.31 |
| | 5 | 2.06 ± 0.31 | 3.37 ± 0.09 | 4.37 ± 0.48 | 2.37 ± 0.17 | 1.31 ± 0.15 |
| | 7.5 | 1.18 ± 0.04 | 2.47 ± 0.07 | 3.11 ± 0.04 | 3.08 ± 0.17 | 6.21 ± 0.28 |
| | 10 | 0.52 ± 0.02 | 2.30 ± 0.12 | 1.04 ± 0.03 | 4.36 ± 0.13 | 0.50 ± 0.03 |

**Table 3a :Tablet Formulation by direct compression method**

| Drug (%) | Binder (%) | Diluent (%) | Lubricant (%) | Disintegrant[a] (%) | | | |
|---|---|---|---|---|---|---|---|
| Folic acid (2) | Avicel PH102 (54.39-37.4) | DCL 21 (40) | Magnesium Stearate (1) | 2.5 | 5 | 7.5 | 10 |

[a]The disintegrant - corn starch or sodium starch glycolate or croscarmellose sodium or crospovidone or HMCD-20, DCL - Dicalcium lactose

**Table 3b: Disintegration Test Results of Tablets Prepared by Direct Compression Method**

| | Disintegrant (%) | Disintegration time (in min) | | | | |
|---|---|---|---|---|---|---|
| | | HMCD-20 | Corn starch | Sodium Starch Glycolate | Cros -carmellose | Crospovidone |
| Hardness 6-8 Kg | 2.5 | 1.11 ± 0.19 | 0.45 ± 0.01 | 2.09 ± 0.70 | 1.28 ± 0.10 | 0.49 ± 0.03 |
| | 5 | 2.37 ± 0.28 | 1.05 ± 0.40 | 2.57 ± 0.50 | 1.08 ± 0.05 | 0.29 ± 0.01 |
| | 7.5 | 2.15 ± 0.04 | 2.30 ± 0.16 | 3.00 ± 0.14 | 1.07 ± 0.03 | 0.32 ± 0.02 |
| | 10 | 3.47 ± 0.30 | 1.33 ± 0.26 | 2.58 ± 0.40 | 1.12 ± 0.02 | 0.50 ± 0.05 |
| Hardness 8-10 Kg | 2.5 | 3.48 ± 0.47 | 3.45 ± 0.45 | 3.55 ± 0.32 | 3.54 ± 0.20 | 2.01 ± 0.26 |
| | 5 | 2.27 ± 0.30 | 2.22 ± 0.14 | 5.21 ± 0.10 | 2.12 ± 0.30 | 0.41 ± 0.04 |
| | 7.5 | 6.20 ± 0.40 | 6.33 ± 0.69 | 5.50 ± 0.25 | 2.24 ± 0.10 | 1.34 ± 0.08 |
| | 10 | 6.34 ± 0.40 | 6.04 ± 0.60 | 5.00 ± 0.17 | 3.66 ± 0.20 | 1.15 ± 0.09 |

**Table 4: Swelling capacity of different degrees of HMCD in water.**

| S.No | Degree of Crosslinking (HMCD) | SWELLING CAPACITY IN WATER | | | |
|---|---|---|---|---|---|
| | | AFTER 15 min | AFTER 30 min | AFTER 1 hr | AFTER 4 hrs |
| 1 | 20 | 12.1 ± 0.10 | 12.0 ± 0.17 | 12.0 ± 0.10 | 12.0 ± 0.10 |
| 2 | 25 | 8.5 ± 0.10 | 8.3 ± 0.00 | 8.3 ± 0.10 | 8.3 ± 0.10 |
| 3 | 30 | 9.1 ± 0.00 | 9.0 ± 0.10 | 9.0 ± 0.00 | 9.0 ± 0.00 |
| 4 | 35 | 8.6 ± 0.20 | 8.5 ± 0.10 | 8.4 ± 0.17 | 8.3 ± 0.00 |
| 5 | 40 | 10.0 ± 0.17 | 10.0 ± 0.20 | 9.7 ± 0.10 | 9.5 ± 0.00 |
| 6 | 45 | 8.3 ± 0.00 | 8.1 ± 0.26 | 8.0 ± 0.20 | 8.0 ± 0.20 |
| 7 | 50 | 7.8 ± 0.20 | 7.8 ± 0.20 | 7.9 ± 0.10 | 7.9 ± 0.10 |

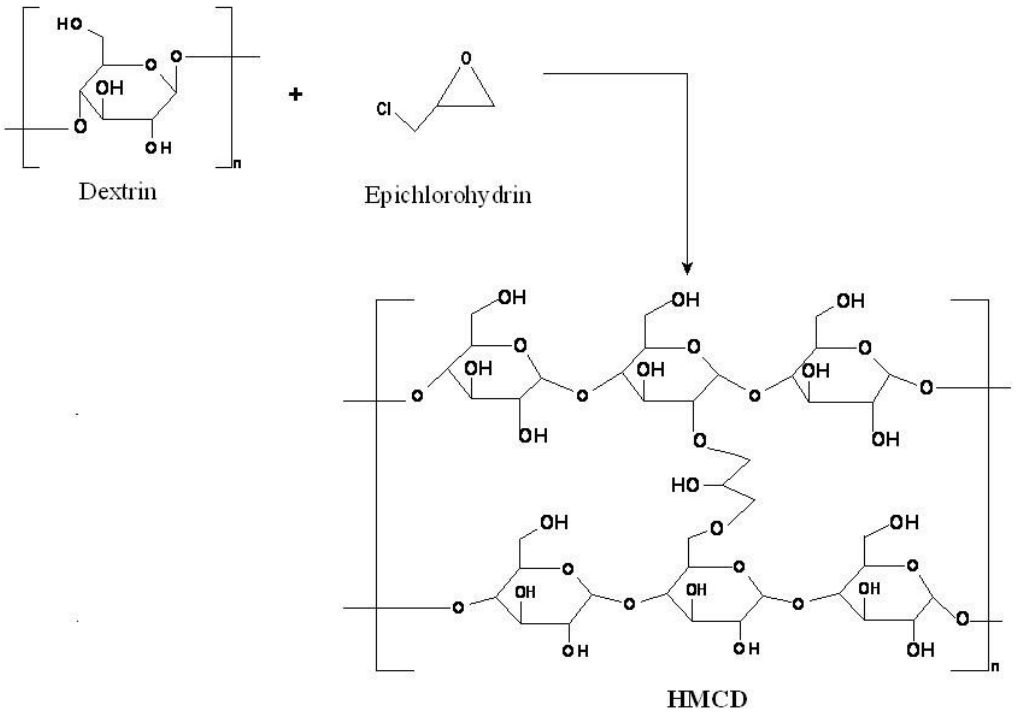



**Fig. 1.** Scheme 1: Reaction of Dextrin with Epichlorohydrin to yield HMCD.

**Results and Discussion**

The two carbohydrate chains present in the dextrin can be linked by a bifunctional linking agent, epicholorohydrin by a covalent bond. In this linkage reaction, the hydroxyl groups of the chains are involved. A typically cross-linked dextrin can be depicted in scheme 1.

2-hydroxymethylene cross-linked dextrin were prepared by the method previously reported (Kota Satyanarayana etal. 2008 WO 2008/117300 A2). Initially dextrin was cross linked with 5-50 % epichlorohydrin by weight to obtain 2-hydroxymethylene cross-linked dextrin having a cross-linking degree ranging from 5 to 50. HMCD with cross linking degree (5-15) was water soluble and white in color where as HMCD with cross linking degree (20-50) was water insoluble and yellowish in color. The yields, appearance and water solubility are shown in table 1. All of the HMCDs were evaluated for swelling power. Dextrin cross-linked with 20% epichlorohydrin by weight has shown highest swelling power. Hence it was selected for detailed evaluation.

**Table 5 : Pre composition parameters and evaluation of tablets prepared by wet granulation method**

| Disintegrant | % of Disintegrant | BD (gm/ml) | TD (gm/ml) | CI % | HR | Hardness 6-8 Kg | | | | Hardness 8-10 Kg | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Hardness ($Kg/cm^2$) | Friability | Weight Variation % | DT (Min±SD) | Hardness ($Kg/cm^2$) | Friability | Weight Variation % | DT (Min±SD) |
| Corn starch | 2.5 | 0.57 | 0.67 | 15.55 | 1.18 | 7.2 | 0.48 | 1.05 | 8.14±0.44 | 8.3 | 0.44 | 0.47 | 11.99 ± 0.4 |
| Sodium starch glycolate | 2.5 | 0.44 | 0.52 | 16.50 | 1.19 | 6.8 | 0.19 | 1.96 | 0.33±0.06 | 8.7 | 0.20 | 1.31 | 1.16 ± 0.23 |
| Croscarmellose sodium | 2.5 | 0.54 | 0.64 | 15.76 | 1.18 | 7.5 | 0.23 | 1.50 | 3.00±0.30 | 8.5 | 0.08 | 0.70 | 5.17 ± 0.10 |
| Crospovidone | 2.5 | 0.45 | 0.58 | 21.64 | 1.27 | 6.5 | 0.70 | 0.37 | 1.22±0.11 | 8.6 | 0.16 | 1.08 | 5.24 ± 0.31 |
| HMCD-20 | 2.5 | 0.51 | 0.61 | 15.98 | 1.19 | 7.1 | 0.39 | 1.36 | 0.56±0.30 | 9.1 | 0.28 | 0.95 | 3.31 ± 0.10 |
| Corn starch | 5 | 0.49 | 0.57 | 14.35 | 1.16 | 7.4 | 0.19 | 1.85 | 1.46±0.06 | 9.4 | 0.51 | 1.03 | 3.37 ± 0.09 |
| Sodium starch glycolate | 5 | 0.57 | 0.70 | 18.36 | 1.22 | 7.9 | 0.27 | 0.12 | 1.18±0.05 | 9.9 | 0.23 | 0.15 | 4.37 ± 0.48 |
| Croscarmellose sodium | 5 | 0.50 | 0.60 | 16.36 | 1.21 | 7.8 | 0.28 | 1.85 | 1.12±0.08 | 8.2 | 0.23 | 1.83 | 2.37 ± 0.17 |
| Crospovidone | 5 | 0.44 | 0.54 | 18.31 | 1.22 | 7.8 | 0.20 | 0.12 | 1.03±0.27 | 8.2 | 0.23 | 1.15 | 1.31 ± 0.15 |
| HMCD-20 | 5 | 0.51 | 0.61 | 16.36 | 1.19 | 7.3 | 0.26 | 1.85 | 0.53±0.24 | 8.4 | 0.28 | 1.11 | 2.06 ± 0.31 |
| Corn starch | 7.5 | 0.48 | 0.55 | 13.17 | 1.15 | 6.7 | 0.35 | 0.86 | 1.66±0.22 | 8.3 | 0.34 | 0.47 | 2.47 ± 0.07 |
| Sodium starch glycolate | 7.5 | 0.39 | 0.48 | 17.84 | 1.21 | 7.6 | 0.46 | 0.84 | 2.27±0.29 | 8.7 | 0.49 | 0.27 | 3.11 ± 0.04 |
| Croscarmellose sodium | 7.5 | 0.44 | 0.51 | 14.40 | 1.16 | 7.4 | 0.22 | 0.86 | 2.37±0.09 | 8.4 | 0.39 | 0.90 | 3.08 ± 0.17 |
| Crospovidone | 7.5 | 0.51 | 0.59 | 13.59 | 1.15 | 6.9 | 0.82 | 0.40 | 3.43±0.07 | 8.1 | 0.62 | 0.84 | 6.21 ± 0.28 |
| HMCD-20 | 7.5 | 0.42 | 0.53 | 19.73 | 1.24 | 7.6 | 0.51 | 0.38 | 0.45±0.07 | 8.1 | 0.39 | 1.31 | 1.18 ± 0.04 |
| Corn starch | 10 | 0.40 | 0.50 | 18.84 | 1.23 | 7.8 | 0.34 | 1.61 | 1.40±0.13 | 8.8 | 0.39 | 0.74 | 2.30 ± 0.12 |
| Sodium starch glycolate | 10 | 0.39 | 0.45 | 13.59 | 1.15 | 7.5 | 0.17 | 2.08 | 0.37±0.05 | 9.5 | 0.38 | 0.68 | 1.04 ± 0.03 |
| Croscarmellose sodium | 10 | 0.53 | 0.64 | 16.92 | 1.20 | 7.3 | 0.16 | 2.16 | 3.20±0.10 | 9.3 | 0.14 | 1.15 | 4.36 ± 0.13 |
| Crospovidone | 10 | 0.42 | 0.49 | 13.87 | 1.16 | 6.4 | 0.33 | 0.80 | 0.33±0.04 | 8.2 | 0.36 | 0.98 | 0.50 ± 0.03 |
| HMCD-20 | 10 | 0.43 | 0.54 | 19.07 | 1.23 | 6.2 | 0.24 | 0.60 | 0.42±0.01 | 9.4 | 0.39 | 2.30 | 0.52 ± 0.02 |

BD: Bulk density, TD: Tapped density, CI: Compressibility Index, HR: Hausner's ratio, DT: Disintegration time

**Table 6: Pre composition parameters and evaluation of tablets prepared by direct compression technique**

| Disintegrant | % of Disintegrant | BD (gm/ml) | TD (gm/ml) | CI % | HR | Hardness 6-8 Kg | | | | Hardness 8-10 Kg | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | Hardness ($Kg/cm^2$) | Friability | Weight Variation % | DT (Min±SD) | Hardness ($Kg/cm^2$) | Friability | Weight Variation % | DT (Min±SD) |
| Corn starch | 2.5 | 0.48 | 0.68 | 30.00 | 1.42 | 6.7 | 0.11 | 0.74 | 0.45±0.01 | 8.9 | 0.078 | 0.68 | 3.45 ± 0.45 |
| Sodium starch glycolate | 2.5 | 0.49 | 0.67 | 26.47 | 1.36 | 6.8 | 0.03 | 0.60 | 2.09±0.70 | 8.2 | 0.03 | 0.40 | 3.55 ± 0.32 |
| Croscarmellose sodium | 2.5 | 0.47 | 0.65 | 27.93 | 1.37 | 6.8 | 0.07 | 0.40 | 1.28±0.10 | 8.5 | 0.03 | 1.80 | 3.54 ± 0.20 |
| Crospovidone | 2.5 | 0.46 | 0.65 | 28.16 | 1.39 | 6.9 | 0.04 | 0.87 | 0.49±0.03 | 8.0 | 0.04 | 0.91 | 2.01 ± 0.26 |
| HMCD-20 | 2.5 | 0.47 | 0.65 | 28.57 | 1.40 | 7.0 | 0.03 | 1.38 | 1.11±0.19 | 8.6 | 0.04 | 0.24 | 3.48 ± 0.47 |
| Corn starch | 5 | 0.46 | 0.68 | 31.94 | 1.46 | 7.2 | 0.07 | 1.70 | 1.05±0.40 | 8.5 | 0.03 | 0.60 | 2.22 ± 0.14 |
| Sodium starch glycolate | 5 | 0.45 | 0.67 | 26.38 | 1.35 | 6.4 | 0.04 | 0.40 | 2.57±0.50 | 8.1 | 0.03 | 0.80 | 5.21 ± 0.10 |
| Croscarmellose sodium | 5 | 0.46 | 0.65 | 30.13 | 1.43 | 6.5 | 0.03 | 0.98 | 1.08±0.05 | 8.3 | 0.04 | 0.58 | 2.12 ± 0.30 |
| Crospovidone | 5 | 0.43 | 0.65 | 33.33 | 1.50 | 6.2 | 0.04 | 1.22 | 0.29±0.17 | 8.4 | 0.03 | 0.74 | 0.41 ± 0.04 |
| HMCD-20 | 5 | 0.47 | 0.65 | 28.16 | 1.39 | 6.6 | 0.08 | 1.60 | 2.37±0.28 | 9.2 | 0.04 | 0.78 | 2.27 ± 0.30 |
| Corn starch | 7.5 | 0.47 | 0.67 | 30.55 | 1.44 | 7.2 | 0.03 | 0.46 | 2.30±0.16 | 9.1 | 0.00 | 0.84 | 6.33 ± 0.69 |
| Sodium starch glycolate | 7.5 | 0.48 | 0.70 | 30.55 | 1.44 | 7.5 | 0.08 | 1.18 | 3.00±0.14 | 9.6 | 0.12 | 0.68 | 5.50 ± 0.25 |
| Croscarmellose sodium | 7.5 | 0.45 | 0.64 | 29.57 | 1.42 | 7.6 | 0.04 | 0.19 | 1.07±0.03 | 8.8 | 0.07 | 0.46 | 2.24 ± 0.10 |
| Crospovidone | 7.5 | 0.45 | 0.66 | 31.42 | 1.45 | 7.1 | 0.35 | 0.40 | 0.32±0.02 | 8.9 | 0.15 | 0.35 | 1.34 ± 0.08 |
| HMCD-20 | 7.5 | 0.47 | 0.66 | 28.16 | 1.39 | 7.4 | 0.04 | 1.09 | 2.15±0.04 | 9.2 | 0.04 | 1.44 | 6.20 ± 0.40 |
| Corn starch | 10 | 0.47 | 0.70 | 32.00 | 1.47 | 7.7 | 0.06 | 0.91 | 1.33±0.26 | 8.9 | 0.08 | 1.08 | 6.04 ± 0.60 |
| Sodium starch glycolate | 10 | 0.49 | 0.69 | 29.33 | 1.41 | 8.0 | 0.12 | 0.47 | 2.58±0.40 | 9.0 | 0.04 | 0.66 | 5.00 ± 0.17 |
| Croscarmellose sodium | 10 | 0.47 | 0.68 | 31.42 | 1.45 | 7.9 | 0.08 | 0.40 | 1.12±0.02 | 9.5 | 0.04 | 0.68 | 3.66 ± 0.20 |
| Crospovidone | 10 | 0.49 | 0.66 | 32.05 | 1.47 | 7.8 | 0.39 | 0.91 | 0.50±0.05 | 8.6 | 0.24 | 0.92 | 1.15 ± 0.09 |
| HMCD-20 | 10 | 0.47 | 0.67 | 30.00 | 1.42 | 7.9 | 0.24 | 0.59 | 3.47±0.30 | 8.4 | 0.16 | 0.58 | 6.34 ± 0.40 |

BD: Bulk density, TD: Tapped density, CI: Compressibility Index, HR: Hausner's ratio, DT: Disintegration time

**Characterization of HMCD**

Dextrin cross-linked with 20% epichlorohydrin (HMCD-20) by weight was selected for detailed evaluation and was characterized as below.

**Fourier Transform Infrared (FTIR) Spectroscopy**

IR spectra of dextrin and 2-hydroxymethylene cross linked dextrin are presented in fig-2 and 2.1. The spectra of dextrin presents bands at 3416 (0-H), 2927(C-H), 1155(C-0), 1016(C-C) $cm^{-1}$ (Fig 2). All the above characteristic peaks appear in the spectra of HMCD-20 at same wavelength except 1420 $cm^{-1}$ peak shifted to 1458-1460 $cm^{-1}$ due to $CH_2$ bends added by cross linking (Fig 2.1).

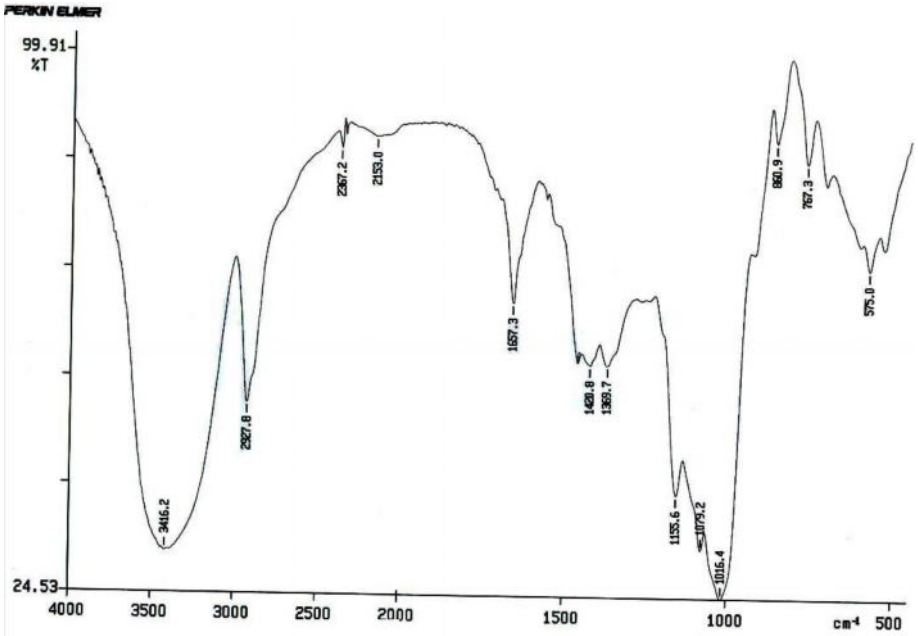



**Fig. 2.** FTIR spectra of Dextrin

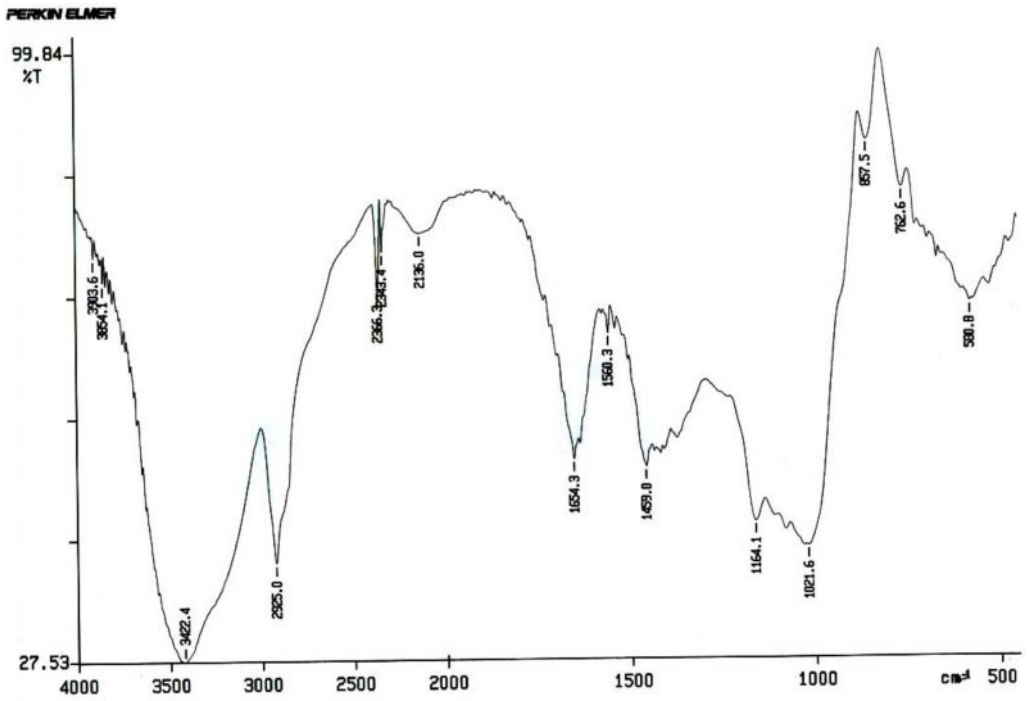



**Fig. 2.1.** FTIR spectra of HMCD-20.

**Differential Scanning Calorimetry (DSC)**

DSC thermographs of dextrin presents three broad endothermic peaks at 91.06, 221.49, 259.04 $^{o}$C (Fig-3). Where as HMCD-20 shows one broad endothermic peak at 102.89 $^{o}$C, which shows that the disappearance of the other endothermic peaks is an indication of change in crystalline structure of HMCD-20 due to cross-linking (Fig 3.1).

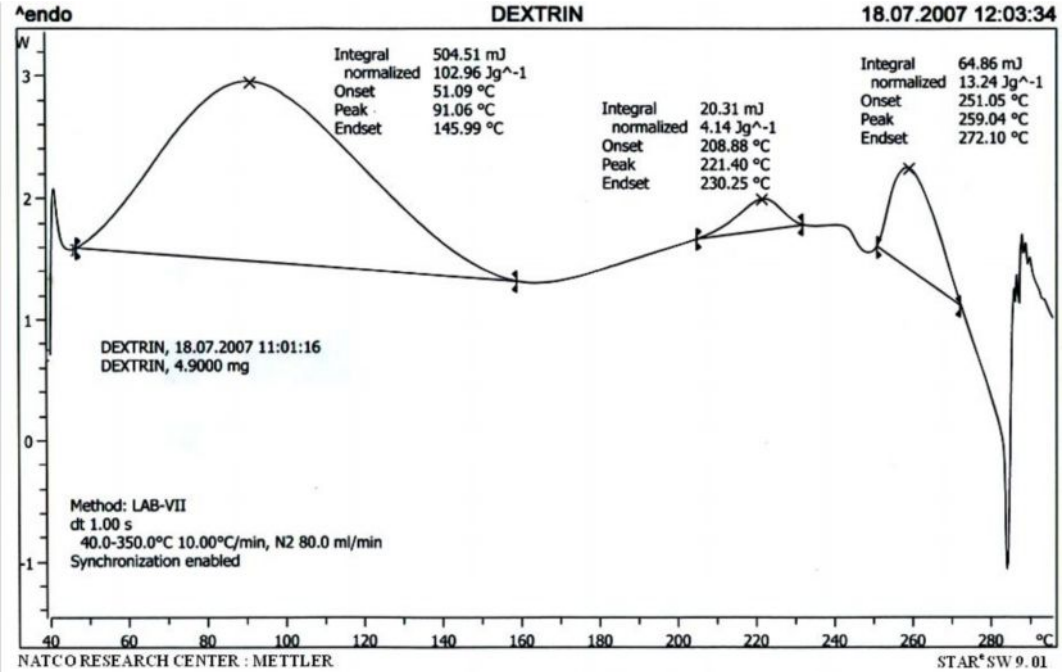



**Fig . 3 . Dextrin DSC trace at 40-280 °C with the heating rate of 10°C/min**

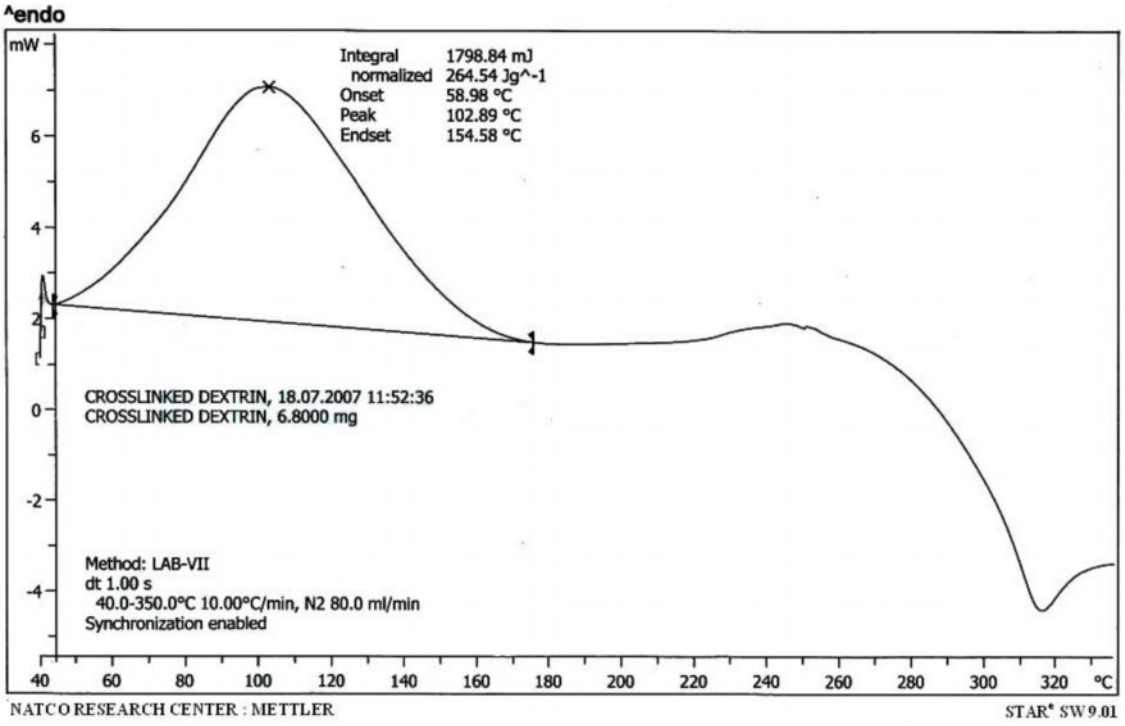



**Fig. 3.1. HMCD-20 DSC trace at 40-320 °C with the heating rate of 10°C/min**

**Maldi**

Dextrin showed peaks at 1200, 1500, 1600, 2700 Daltons whereas 2-hydroxymethylene cross-linked dextrin showed peaks at 2700, 2800, 3000, 3200 and 4100 Daltons (Fig 4).

The mass values of these peaks are about twice to dextrin mass value which clearly indicates cross-linking (Fig 4.1).

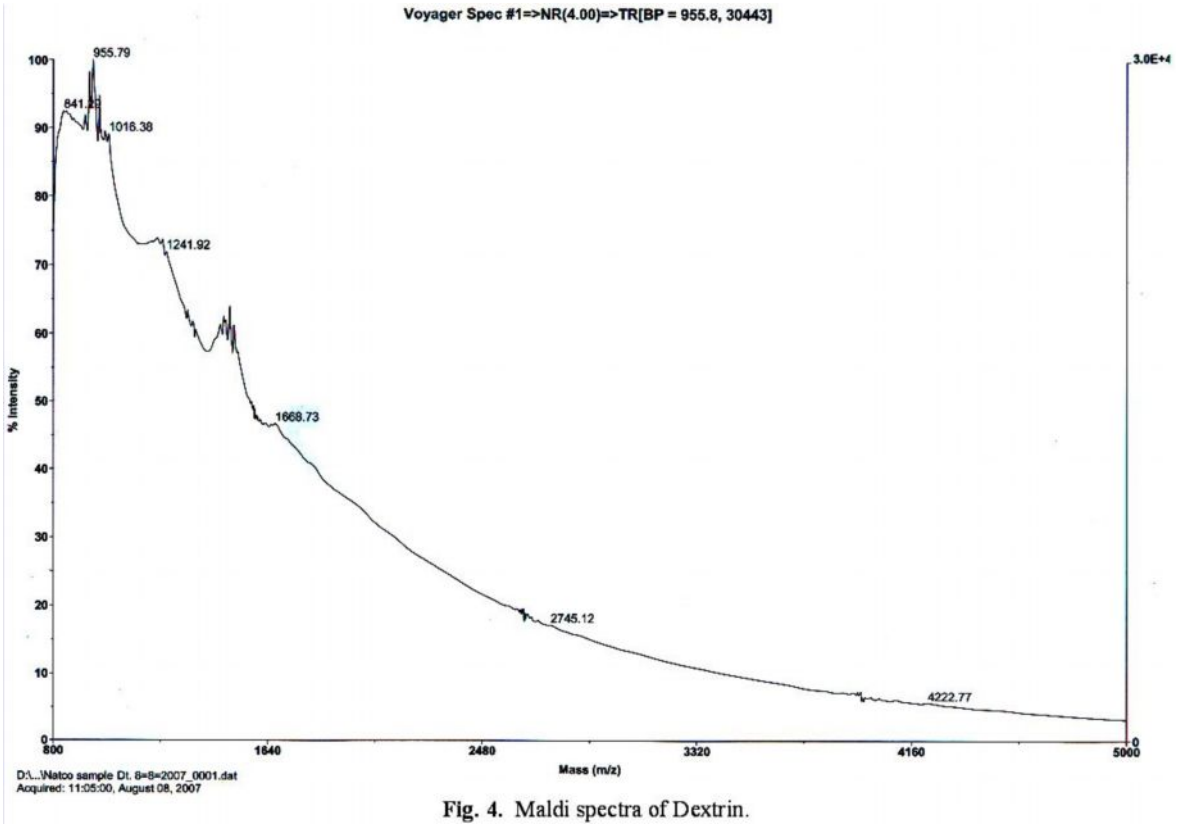



Fig. 4. Maldi spectra of Dextrin.

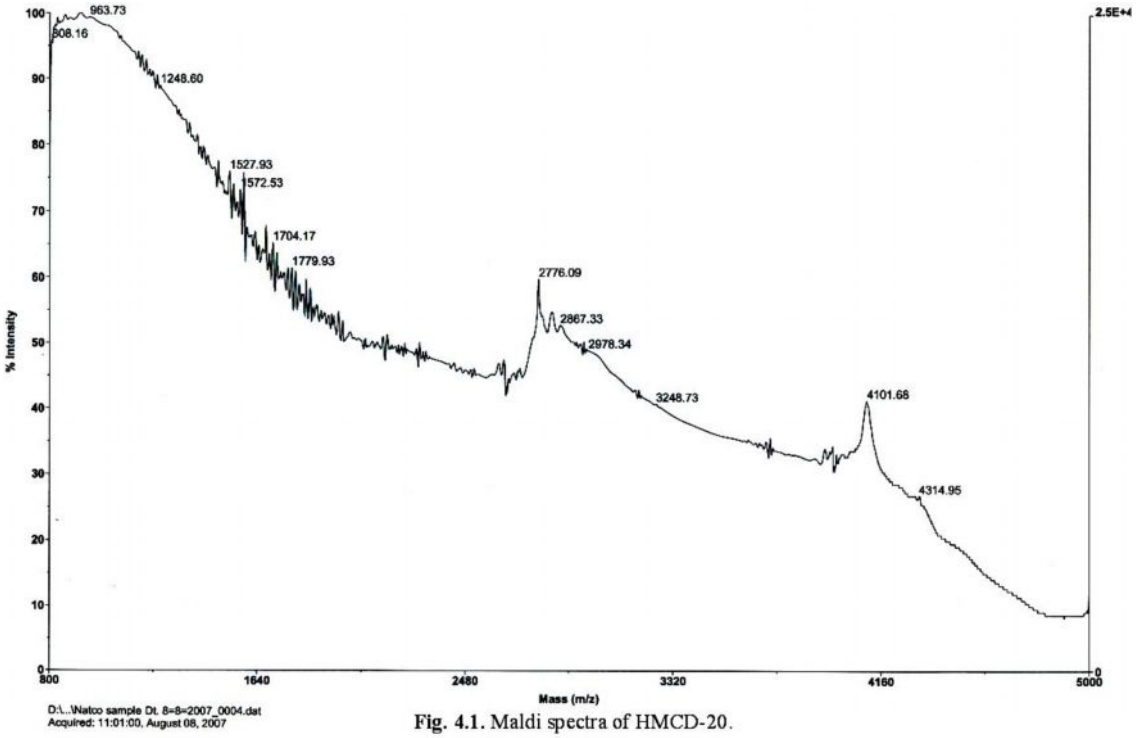



**Fig. 4.1.** Maldi spectra of HMCD-20.

**Swelling capacity of HMCD**

2-Hydroxymethylene cross-linked dextrins with 5-15% epicholohydrin were water soluble and those with 20-50 were water insoluble. Among HMCD's with varying degree of cross-linking, the HMCD-20 showed highest swelling capacity (12 ml) (Table-4). This also possesses proper balance of hydrophilicity and hydrophobicity. Hence it was chosen for further studies.

**Acute toxicity studies**

To determine the safety and suitability of HMCD-20 for oral delivery, acute toxicity studies were carried out by giving HMCD-20 suspension in normal saline orally at a dose of 100, 500, 1000, 2000 mg/kg body weight and the animals were observed continuously for behavioral changes for the first 4 hrs and then for mortality rate for 72 hrs. The negative control animals were fed with normal saline. No significant behavioral changes were observed in first 4 hrs and no mortality in 72 hrs.

**Evaluation of Disintegrating Property of 2-Hydroxymethylene Cross-Linked Dextrins in Tablets prepared by Wet Granulation Technique and by Direct Compression Method**

The highest swelling property was observed with HMCD-20; hence studies were conducted with HMCD-20. Tablets are generally prepared by wet granulation and direct compression methods. Hence, the newly synthesized HMCD-20 was evaluated for disintegrating property by wet granulation technique using paracetamol as model and direct compression using folic acid.

Five formulations of paracetamol and folic acid were prepared with varying concentration of the five disintegrants: corn starch, sodium starch glycolate, croscarmellose sodium, crospovidone and HMCD-20. For each formulation, blend of drug and excipients were prepared. Since, the flow properties of the powder mixture are important for the uniformity of mass of the tablets, the flow of the powder mixture for each formulation was analyzed before compression to tablets.

In case of paracetamol granules the bulk density was found in the range of 0.394 – 0.578 gm/ml and the tapped density between 0.456 and 0.708 gm/ml. Using these two-density data Hausner's ratio and Compressibility Index were calculated. The powder blends of all the formulations had Hausner's ratio of 1.27 or less indicating good flowability. The Compressibility Index was found between 13.17 and 21.64 % and the compressibility- flowability correlation data indicated a fairly good flowability of the powder blend (Table-5).

In case of folic acid tablets, bulk density was found to be between 0.439 to 0.514 gm/ml and tapped density between 0.644 to 0.766 gm/ml, Compressibility Index between 26.38 to 34.66 %, Hausner ratio between 1.35 to 1.5. Compressibility- flowability correlation data indicated poor flowability of the powder blend (Table-6).

Tablets were prepared using wet granulation & direct compression technique. Tablets obtained were of uniform weight due to uniform die fill, with acceptable weight variation as per pharmacopoeial specification. Hardness of all the formulations was measured in $kg/cm^2$. The hardness of all formulations was found to be 6-8 $kg/cm^2$ and 8-10 $kg/cm^2$.

Friability values of all the formulations were within the limit i.e. less than 1.0% indicated that tablets had a good mechanical resistance. Results of post compression parameters are shown in table 5, 6.

HMCD-20 was evaluated for its disintegration property by wet granulation method and direct compression technique.

In wet granulation method, paracetamol was used as an active constituent with a disintegrant concentration of 2.5-10.0%. At a compressional strength of 6-8 kg and disintegrant concentration of 2.5-10.0%, the disintegration time exhibited by HMCD-20 was less than 1 min. At 2.5% concentration HMCD-20 (0.56 ± 0.30 min) was found to be 10 times more potent than corn starch (8.14 ± 0.44 min) and more potent than superdisintegrants like croscarmellose (3.00 ± 0.30 min) and crospovidone (1.22 ± 0.11 min). At a compressional strength of 8-10 kg, HMCD-20 (3.31 ± 0.10 min) was found to be 3 times more potent than corn starch (11.99 ± 0.4 min) and about 1.5 times more potent than croscarmellose (5.17 ± 0.10 min), crospovidone (5.24 ± 0.31 min).

In direct compression technique, tablets were formulated with HMCD-20 and other superdisintegrants at a concentration of 2.5-10% using folic acid as an active constituent. At a compressional strength of 6-8 kg and at a concentration of 2.5%, corn starch and HMCD-20 exhibited disintegration time of 0.45 ± 0.01 min and 1.11 ± 0.19 min. All the other superdisintegrants like sodium starch glycolate, croscarmellose, crospovidone exhibited a disintegration time of 2.09 ± 0.70 min, 1.28 ± 0.10 min, 0.49 ± 0.03 min respectively. At a compressional strength of 8-10 kg and at a concentration of 2.5%, corn starch and HMCD-20 exhibited a disintegration time of 3.45 ± 0.45 min and 3.48 ± 0.47 min. All the other superdisintegrants like sodium starch glycolate, croscarmellose, crospovidone exhibited a disintegration time of 3.55 ± 0.32 min, 3.54 ± 0.20 min, 2.01 ± 0.26 min respectively. The results of disintegration time are shown in table 2b & 3b.

Disintegration property of HMCD-20 was found to be similar to other marketed superdisintegrants when formulated by wet granulation method. Hence 2-hydroxymethylene cross-linked dextrin (HMCD-20) can be categorized as a novel, non-ionic, non-hygroscopic, starch based superdisintegrant.

## Conclusion

Cross-linking of hydrophilic dextrin with epichlorohydrin induces hydrophobicity, which in turn induces swelling property to dextrin. Amongst dextrin cross-linked with various proportions of epichlorohydrin, 20% (HMCD-20) has shown best swelling property and it possessed proper blend of hydrophobicity and hydrophilicty, hence it was selected for evaluation of tablet disintegrant property. HMCD-20 exhibited disintegration time of less than 1 minute in wet granulation technique. Its disintegration time was 4 times to superdisintegrant crosscarmellose at 2.5% disintegrant concentration. In direct compression methodology, HMCD-20 disintegrant profile is similar to other superdisintegrants. 2-Hydroxymethylene cross linked dextrins is novel class of starch-based superdisintegants, which are non-ionic in nature prepared from commercially abundantly and cheaply available raw material dextrin.

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