

Appendix I

I.1 Related materials

I.1.1 Carbomer 934P

Carbomers are carboxyvinyl polymers of extremely high molecular weight that are available as dry fluffy powders. Various grades of carbomers are commercially available that differ from each other depending on their molecular weight and architecture as well as on the use of either allylsucrose or allylethers of pentaerythritol for cross-linking acrylic acid. The chemical structure of carbomer is illustrated in Fig. I.1.

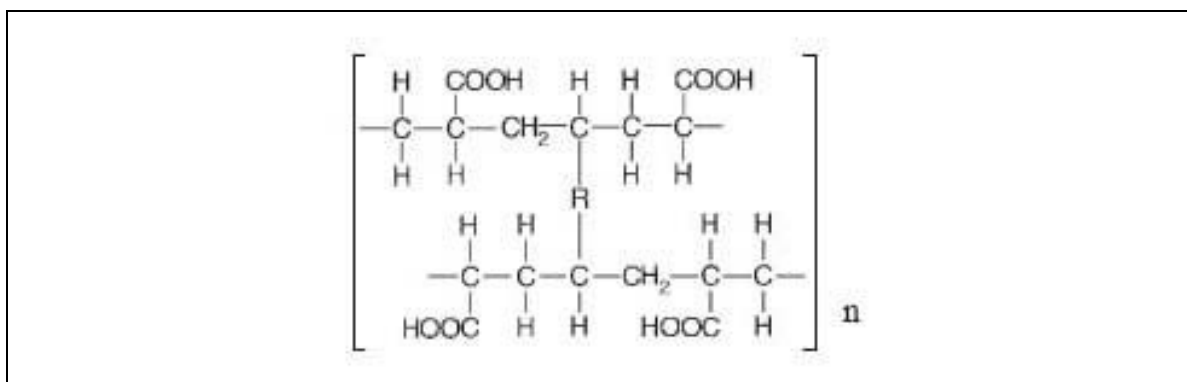


Fig. I.1: The structure of Carbomer (R= allylsucrose or allyl pentaerythritol) [8]

Carbomer resins intended for oral and mucosal applications are designated by a 'P' (934P, 974P, 971P) [5, 8-11]. They contain between 56-58% of the carboxylic groups calculated on dry basis. A high percentage of carboxylic acid groups allow the polymer to be water swellable. When dispersed in water, carbomer resin molecules partially swell and become viscous. On neutralization with a water-soluble base, the resin molecules swell completely, with a dramatic increase in their viscosity [47, 54, 57].

Carbomers are extensively being used in the pharmaceutical and cosmetic industry due to:

- excellent thickening efficiency even at low resin concentration, allowing it to be used for suspending insoluble substances and viscosifying and stabilizing emulsions, pastes, ointments, jellies, and the like
- excellent temperature stability even when subjected to heating and cooling cycles
- microbial resistance since dry powder forms of the resin do not support the growth of molds and fungi [5, 8-13].

I.1.2 Microcrystalline cellulose (MCC)

Microcrystalline cellulose is purified, partially depolymerized cellulose that occurs as a white-colored, odorless, tasteless, crystalline powder composed of porous particles [85, 100]. It is commercially available in different particle size grades which have different properties and applications. The structure of microcrystalline cellulose is shown in Fig. I.2.

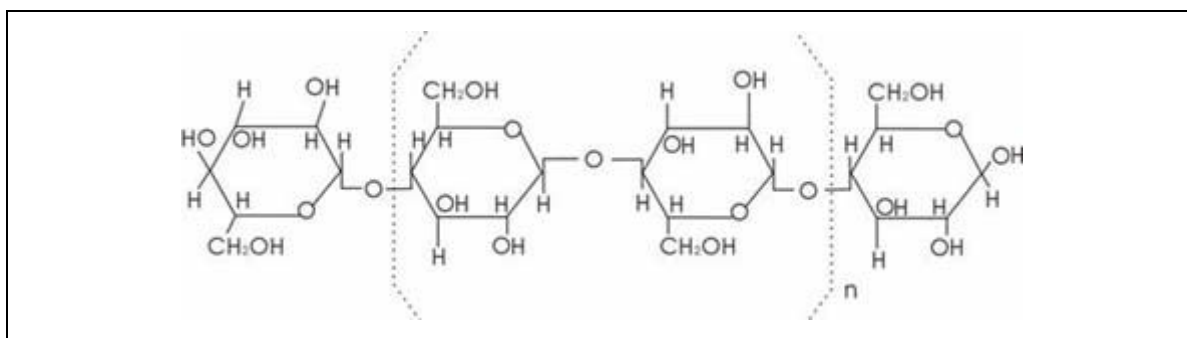


Fig. I.2: The structure of microcrystalline cellulose (MCC) [85]

It is manufactured by the controlled hydrolysis, with dilute mineral acid solutions, of α -cellulose, obtained as a pulp from fibrous plant materials. Following hydrolysis, the hydrocellulose is purified by filtration and the aqueous slurry is spray-dried to form dry, porous particles of a broad size distribution. Several different grades of microcrystalline cellulose are commercially available which differ in their method of manufacture, particle size, moisture, flow and other physical properties. The larger particle size grades generally provide better flow properties in pharmaceutical machinery. Low moisture grades are used with moisture-sensitive materials [100].

Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a nontoxic and nonirritant material. It is not absorbed systemically following oral administration and thus has little toxic potential.

In pharmaceuticals, it is widely used primarily as a diluent in oral tablet and capsule formulations where it is used in both wet granulation and direct compression processes. In addition to its use as a diluent, microcrystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting [85, 100].

7.1.3 Other substances

Other substances used in all investigations are listed in table I.1.

Tab. I.1: Other substances used

Name	Abbreviation	Supplier
Bentonite	Bentonite	Carl Roth GmbH (Quellton)
Calcium chloride Hexahydrate	CaCl ₂ x 6 H ₂ O	Merck AG
Corn starch	Corn starch	Cerestar
Crospovidone	Polyplasdone XL	Polyplasdone XL 10, ISP
Di-Calcium phosphate	Di-Ca-Phosph.	Dicalciumphosphat, Budenheim
Lactose	Lactose	Tablettose 80, Meggle
Magnesium stearate	Mg-Stearate	Merk AG
Polyethylene glycol	PEG 6000	PEG 6000, Merk-Schuchardt
Polyvinylpyrrolidone K 90	PVP K 90	Polyvinylpyrrolidone 350, Serva
Sodium chloride	NaCl	Merck AG
Sodium citrate	Na citrate	Isocommerz
Sodium sulfate Decahydrate	Na ₂ SO ₄ x 10 H ₂ O	Isocommerz
Talc	Talc	VEB Laborchemie Apolda
Theophylline	Theophylline anhydrous	Boehringer Ingelheim
Tricalciumphosphat	Tri-Ca-Phosph.	Tricalciumphosphat, Budenheim

I.2 Methods

I.2.1 Chelate titration method

Since tri-calcium phosphate is almost insoluble in water, it was assumed that its anti-tack action to carbomer is not because the influence of its Ca ions. In order to elucidate this hypothesis, the amount of Ca ions in the composition was measured by the chelate titration method.

The composition contains 30% (w/w) of tri-calcium phosphate, and 1ml of water / 1g of powder were required to prepare wet mass. That is, 1ml of water contains 0.3g of tri-calcium phosphate. Therefore, 0.3 g/ml of tri-calcium phosphate dispersion was prepared and stirred for 30min. After centrifugation, 300ml of solution was prepared and 1N-NaOH was added. This solution was titrated with 0.1N-EDTA solution. Eriochrome black T was used as an indicator. 0.5ml of EDTA solution was required to reach the endpoint (pink → blue color).

1ml of EDTA solution = 4.008 mg Ca

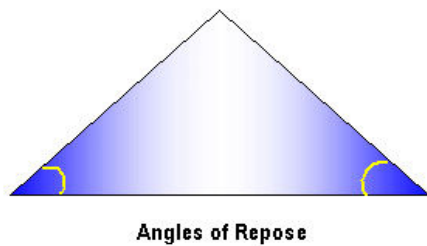
Therefore, 0.5 X 4.008 = 2.004 mg Ca in 300 ml solution

Finally, 1ml of this solution contains 0.006 mg Ca.

I.2.2 Determination of flow rate of powder

50g of powder blends were filled in a glass funnel fixed on a clamp. The time was recorded from when the powder started to flow until finish. Flow rate was calculated as g/s [306]. The mean of five replicates was used as the result.

I.2.3 Determination of angle of repose of powder



Angle of repose is defined as the angle of the free surface of a pile of powder to the horizontal plane [Fig. I.3] [221, 306]. 50g of powder blends were flown from a funnel and the height (h) of the powder cone and radius (r) was measured. Angle of repose was calculated using the equation: $\tan \alpha = h/r$. The mean of five replicates was used as the result.

Fig. I.3: Angle of repose

I.2.4 Determination of enslin number of powder

Enslin number is defined as the absorbed water amount (g or ml) by 1g of substance powder for 15 min. 1g of sample powder was placed in an enslin-apparatus [Fig. I.4], the absorbed water amount was written in 15min [306].

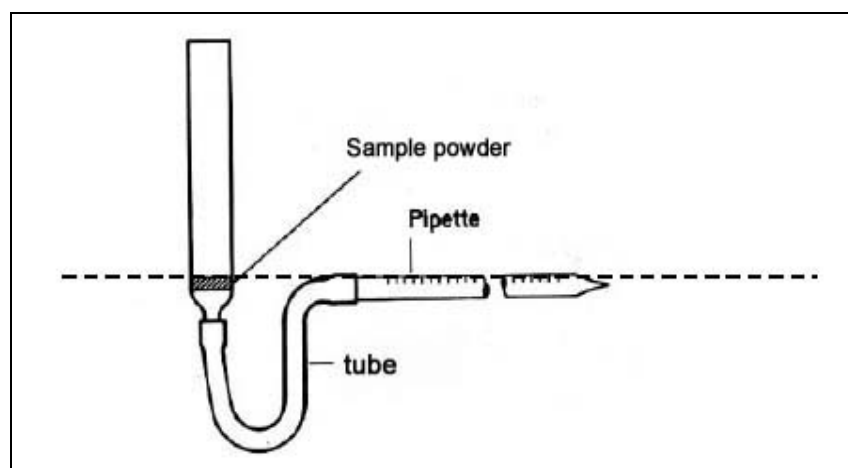


Fig. I.4: Measurement of enslin numer by Enslin-apparatus [306]

I.2.5 Evaluation of pellets

I.2.5.1 Sieve analysis

Particle size distribution was determined by sieve analysis. 100g of sample was sieved using a vibratory sieve shaker (Vibro, Retsch, Germany) at an amplitude 50 for 10min. 2000, 1700, 1400, 1180, 1000, 710, 500, 355, 250, 125, and 90 μ m sieves were used and the fraction retaining on each screen was weighed and expressed as a percentage of the total weight.

Total yield and the yield of sieve fraction 500~1180 μ m were calculated. All results presented are the mean of three determinations. Mass median diameter was the spheroid diameter at the 50-percentile mark on a cumulative percent oversize plot.

Granule yield is involved to determine the quantity of granulated product actually available, thus excluding losses due to sticking to the sides of the bowl (related to static electricity) and the fine particles clogging the filters. The mass of granules obtained at the end of the operation was related to the theoretical quantity.

I.2.5.2 Image analysis

The sphericity, roughness, and aspect ratio of pellets were determined by optical microscopic image analysis using the system Leco IA 3.11(Leco Instrumente GmbH, D-Kirchheim). The basic principles of image analysis system are described in detail in the study of LINDNER und KLEINEBUDDE [307].

400~600 pellets from every batch (sieve fraction 710~1000 μ m) were collected and analyzed. Pellets were dispersed carefully on the microscope slides and a top light source was used to reduce the influence of shadow on the image processing. The image analyzer consisted of a computer system linked to a black/white-video camera, and a stereomicroscope. The digitized images were analyzed by Scion image analyzing software. The Sphericity or roundness (R), and the aspect ratio are defined as follows:

$$R = 4\pi A/C^2 \quad (A = \text{area}, C = \text{circumference})$$

$$\text{Aspect ratio} = d_{\max}/d_{\min} \quad (d_{\max}: \text{the longest Feret diameter}, d_{\min}: \text{the shortest Feret diameter})$$

For a perfect spherical shape, aspect ratio is equal to 1.

I.2.5.3 Determination of density

The bulk density of each batch of pellets was measured by carefully pouring an accurately weighed 50g sample through a funnel into a graduated 250ml cylinder and was calculated by dividing the

weight of the material (g) by the volume (ml) occupied in the cylinder. The cylinder was then tapped 10, 500, 1250 times on a tapping device and the tapped density was also determined in g per ml. The tap setting was sufficient in all cases to reach a constant volume [306].

I.2.5.4 Friability

10g pellets of 710~1000 μ m fraction were rotated with 200 glass beads (4mm in diameter) in friabilator (TAR, Erweka, Germany) at 20rpm for 30min [165]. The glass beads were then removed, and the fine particles were sieved off, the weight loss was calculated as % friability. The results were mean of triplicates.

I.2.5.5 Hardness

Hardness test was performed by measuring of required crushing force using texture Analyzer (EZ-tester, Shimadzu, Japan). 10 pellets of each batch (710~1000 μ m fraction) were tested at following test conditions: a speed to perform of 1mm/min, speed of 10mm/min during the test.

I.2.5.6 Moisture content

Moisture content of pellets were measured during and after granulation process using IR-balance (Type MA 40, Sartorius, Germany) set a temperature of 105°C. The sample was heated to 105°C, and evaporative moisture losses were recorded by the internal balance and automatically reported as percent moisture content.

I.2.5.7 Powder layering efficiency

Powder layering efficiency was calculated by dividing the actual weight gain of coated samples divided by the theoretical weight gain and multiplying by 100 [183, 184]. Theoretical drug content was calculated by dividing the amount of drug present in the layering powder with the total of charge load and the amount of the powder layering composition used.

I.2.5.8 Assay of drug content

Quantities (400 mg) of each batch of pellets were accurately weighed, ground to a fine powder using a pestle and mortar and made up to 1000 ml of water and allowed to stand for 1h. Aliquots of the solutions were filtered and assayed spectrophotometrically for theophylline at 271.

I.2.5.9 Dissolution test

I.2.5.9.1 Standard curve of model drug (theophylline)

10mg of theophylline was dissolved in 1L of medium (demineralized water, pH 3 and pH 6.8 phosphate buffer solution). This solution was diluted to $0,2 \times 10^{-2}$, $0,3 \times 10^{-2}$, $0,5 \times 10^{-2}$, and $0,8 \times 10^{-2}$ mg/ml and UV absorbance was measured. The mean of three replicates was used as the result. The results are shown in Fig. I.5~ I.7.

I.2.5.9.2 Dissolution test

Dissolution test was performed according to USP paddle method in 900ml of dissolution medium (purified water, pH 3 and pH 6.8 phosphate buffer solution). 50mg of pellets were used for test. The temperature of the medium was kept $37 \pm 0,5^{\circ}\text{C}$ while the rotational speed of the paddles was set at 50rpm. 5ml samples were withdrawn at regular time intervals and spectrophotometrically determined at 271nm. The mean of three replicates was used as the result.

I.2.5.9.3 Preparation of buffer solution

pH 3 phosphate buffer solution

3.40g of potassium dihydrogen phosphate were dissolved in demineralized water, and the pH value was adjusted with phosphoric acid. This solution was made up to 1000ml by the addition of demineralized water.

pH 6.8 phosphate buffer solution

5.94g of disodium hydrogen phosphate dihydrate and 4.54g of potassium dihydrogen phosphate were dissolved in demineralized water. This solution was made up to 1000ml by the addition of demineralized water.

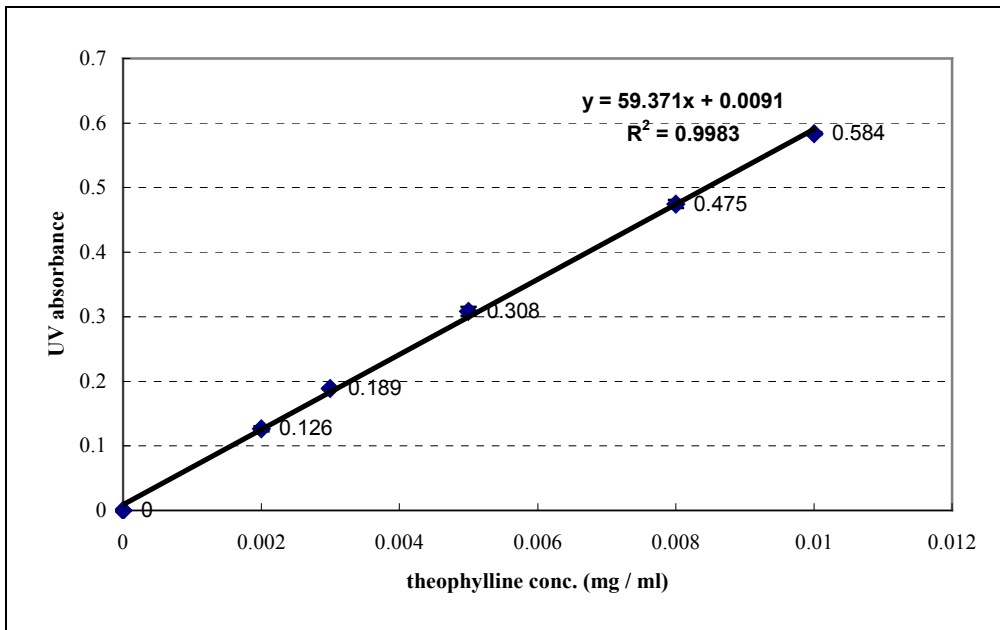


Fig. I.5: standard curve of theophylline in water (pH 3.8) (Mean±S.D., n=3)

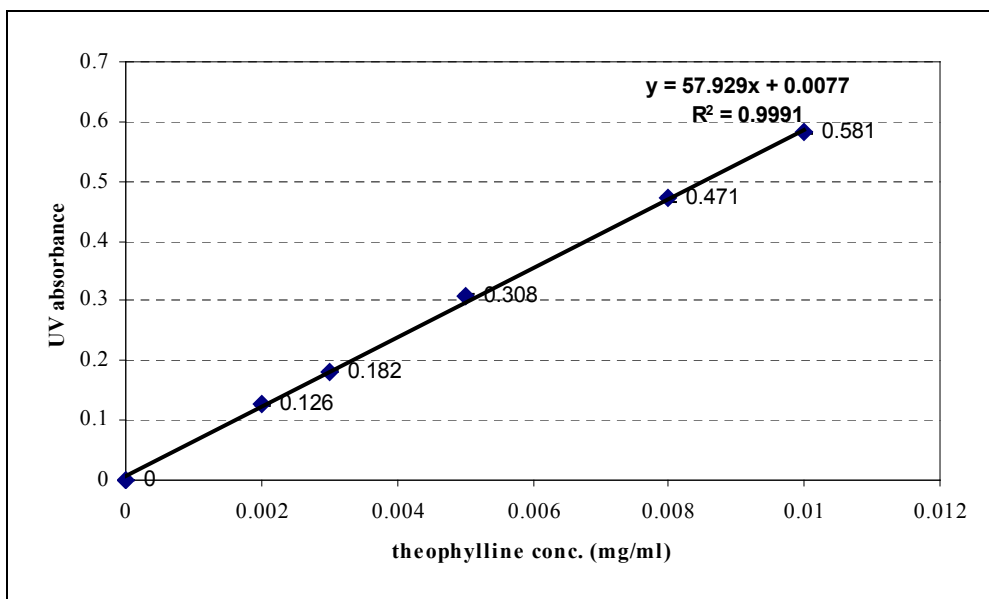


Fig. I.6: standard curve of theophylline in pH 3 phosphate buffer solution (Mean±S.D., n=3)

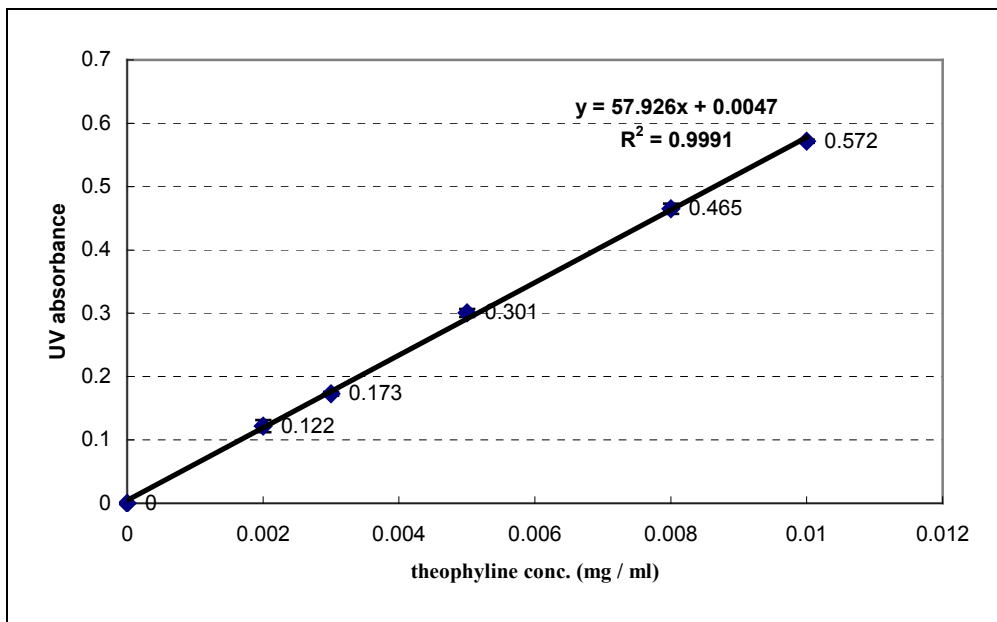


Fig. I.7: standard curve of theophylline in pH 6.8 phosphate buffer solution (Mean \pm S.D., n=3)

Appendix II

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