"BABEŞ-BOLYAI" UNIVERSITY

FACULTY OF PHYSICS

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Rheological and spectroscopical study of some polymeric systems of pharmaceutical interest

PhD Thesis Summary

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Keywords: Rheology, Raman spectroscopy, poly(ethylene oxide), Carbopol, clotrimazole, polymer matrix.

Introduction

Development of new classes of drugs requires the knowledge of the properties of all components of a pharmaceutical product. It is also necessary to understand the chemical and physical interactions between these components, respectively the interactions that occur when they are prepared and also the evolution in time of the components included in the final product. This research can not be achieved only by classical methods, specific to a single field of science, such as pharmaceuticals. It requires various investigation techniques, performed with modern physical methods, to study all the pharmaceutical compounds that are used in the final product and also their evolution in time in different conditions of temperature and humidity.

In this study we examined the physical properties of some polymeric gels that include an active component in their matrix, by rheological, spectroscopic and electrical investigations. The polymers used are: PEO poly(ethylene oxide), with two molecular weights, and Carbopol (polyacrylic acid). As active drug substance we used clotrimazole *(1- [(2 - clorofenil) difenilmetil] – 1H-imidazol)*. The final product is a local pharmaceutical antimycotic, applicable on skin or mucosal tissues. The final product must be biocompatible, stable in time and without aggression on the tissue, allowing the controlled release of the active substance.

The chose of these substances is not accidental, since these polymers are among the most used in the pharmaceutical industry and many aspects of their interaction with other drugs and biological systems are already known.

In the first part of the work we analyzed the general theoretical issues related to polymeric gels. The second part will detail the experimental results achieved through electrical, spectroscopic and rheological investigations. This paper ends with the conclusions arising from this study and with the annexes for each type of investigation.

Polymeric Gels

In general, a gel is formed by interconnecting polymeric chains together, through nodes or points of cross-linking and has an appreciable lifetime [1]. Interconnecting chains can be achieved by physical or chemical processes and the final properties of the obtained network depend essentially on the production and type of such cross-linking points.

1. Temporary gels. They are formed by systems with a high concentration of polymeric segments, by simple topological rearrangement caused by the formation of temporary and mechanical nodes, between polymeric chains.

2. Covalent gels (chemical gels) are formed by reticulation of free covalents of the preexistent chains in sample or by polymerization of monomers, of which at least some have a greater functionality or at least equal to two.

3. Physical gels are systems that fall between the two above. Consist of physical chains (nodes), interconnected between them. These links are characterized by low energy, comparable to thermical energy kT and may have limited or very long life.

4. Gels of pharmaceutical interest: Gels in this category are only those polymeric systems that have the following characteristics: have a good chemical and physical stability, are not toxic to the body, have a good biocompatibility with tissues that come into contact, can easily be eliminated from the body, not chemically interact with drug substance and dissolve in organic solvents that are well tolerated by living organisms, preferably in water.

II. Rheological and electrical study of PEO and Carbopol matrices

2.1 Rheological study of PEO and Carbopol polymeric matrices

For medical applications, some properties of these products are of great importance, namely: good flexibility, controlled disposal [5.6]. These properties should be investigated in the standard human body temperature and temperature limitations incurred by living cells from different tissues. It is important to study these systems in terms of thermal shock and mechanical stress. Quantitative description of these properties is based on measurement of rheological parameters, including viscosity, which plays an important role [7].

2.1.1.Materials and equipment used

The samples investigated were poly(ethylene oxide) PEO1105 PEO750 with molecular weight 75,000 g / mol, respectively 110 500 g/mol pure and polyacrylic acid Carbopol 940 and 980 with two molecular weights 104 400 g/mol, respectively 1 021 317 g/mol. All these polymeric gels were obtained with concentrations between 0.5% and 10% by mixing them with double distilled water.

Viscosity of these samples was measured at different shear rates between 0 and 200 rpm with a Brookfield DV-II Pro+ viscosimeter. Measurements were performed in the temperature range 26-55° C.

2.1.2. Effect of concentration.

The first report was intended with the behavior of viscosity of non-thermal treated aqueous PEO gels depending on temperature and polymeric concentration. It was proposed and tested a mathematical algorithm to analyze the data, based on specific law of Newtonian behavior and on Power law, specific to non-Newtonian behavior.

After analyzing the experimental data, is observed that the fluid passes from non-Newtonian behavior, $n = 1.32$ shear-thickening ($n > 1$) to concentration of 3% to Newtonian behavior, $n \approx 1$ at concentration of 5% and temperature 55° C, then to the non-Newtonian behavior (shear-thinning), $n < 1$ for concentrations higher than 5% Figure 2.2. Both temperature and concentration affect the value of viscosity, but

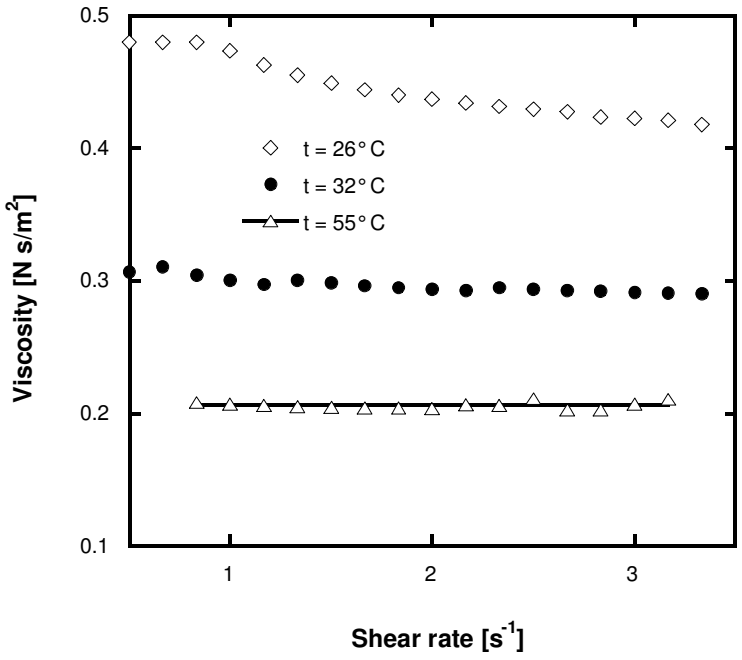

Fig. 2.2. Viscosity Vs. shear rate, for PEO 750 with 5% concentration sample at different temperatures.

concentration's influence is dominant. Increasing concentration facilitates the production of connections between the chains and the gel state extension to higher domains in the sample. Rheological behavior of the sample is described by a power model.

2.1.3 Influence of molecular weight on the rheological behavior of PEO

Further, is studied the behavior of polymeric matrix of PEO 1105 with molecular weight 105,000 g/mol. It is noted that the transition effect of flow from Newtonian behavior to the Non-Newtonian behavior appears when concentration is 3% instead of 5%, as the PEO 750 sample was. Figure 2.8.

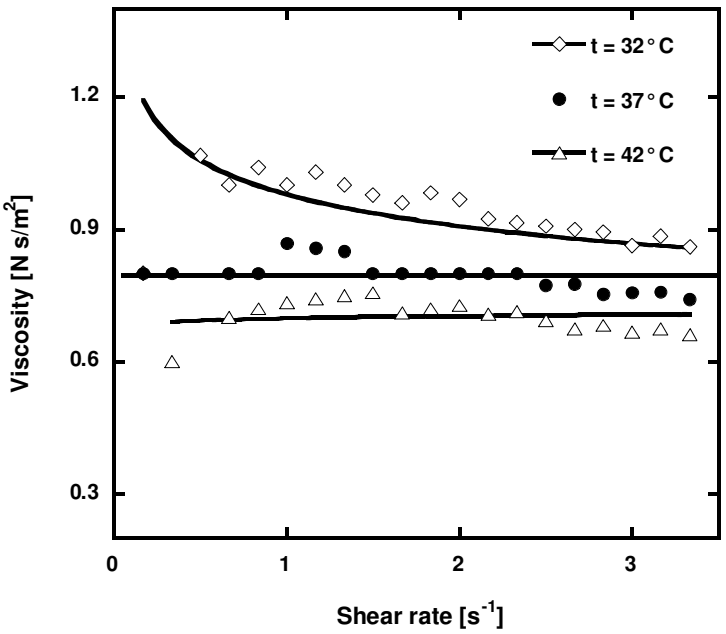

Fig. 2.8. Viscosity Vs. shear rate, for PEO 1105 with 3% concentration, sample at different temperatures.

The decrease of viscosity depending on temperature was observed for all samples of PEO, regardless of molecular weight. Changes in viscosity depending on shear rate shows different types of flow, shear-

thinning ($n < 1$), shear-thickening ($n > 1$) and Newtonian, depending on temperature and polymer concentration.

Transition from shear-thinning ($n < 1$) to shear-thickening ($n > 1$) is mainly determined by polymer concentration. Newtonian flow type was observed for both samples, but this behavior occurs at low concentration of high molecular weight sample, compared with low molecular weight sample. To the non-Newtonian regime, rheological behavior of samples is described by a power law.

2.1.4. Influence of thermal treatment on polymeric matrices.

Thermal treatment was performed by immersion in liquid nitrogen, and then the sample was left 24 hours to return to the initial temperature. Thermal treatment processes were performed on aqueous gels of PEO

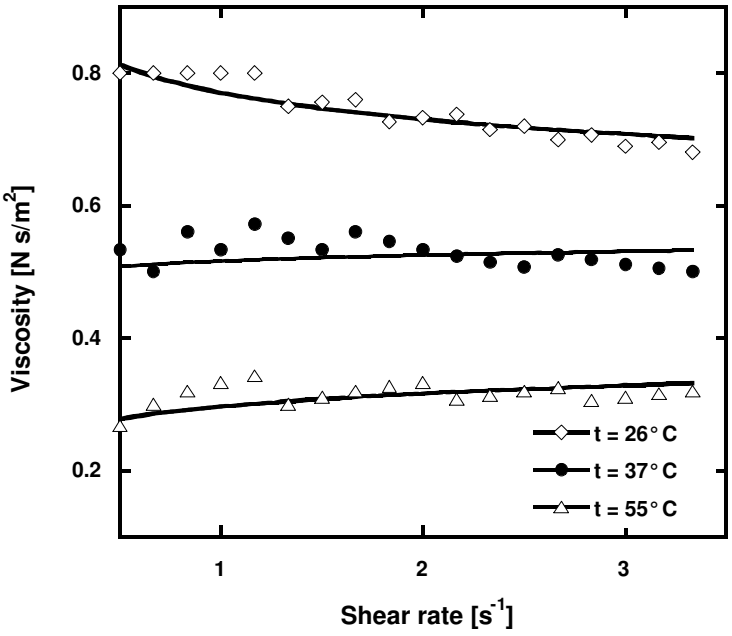

Fig. 2.13.Viscosity Vs. shear rate, for PEO 750 with 5% concentration, thermally treated, sample at different temperatures.

Table 2.4. Experimental and calculated values for PEO 750 gel's rheological parameters, thermally and non thermally treated, with concentrations 3%, 5%, 7% and 9%.

Sample	$t\ (^0C)$	$a\ (Ns/m^2)$		x		X_{av}		n		$a^*(Ns/m^2)$	
		untreated	treated	untreated	treated	untreated	treated	untreated	treated	untreated	treated
PEO 750 3%	55	0.03	0.41	0.39	0.51	0.32	0.44	1.32	1.44	0.03	0.28
	37	0.05	0.87	0.36	0.40					0.05	0.53
	26	0.07	1.16	0.21	0.41					0.06	0.75
PEO 750 5%	55	0.20	0.78	0.04	-0.02	-0.02	-0.08	0.97	0.92	0.21	0.82
	32	0.30	1.36	-0.03	-0.12					0.30	1.32
	26	0.46	1.78	-0.08	-0.11					0.44	1.73
PEO 750 7%	42	1,04	1.5	-0.10	-0.1	-0.11	-0.12	0.89	0.88	1.02	1.57
	37	1,17	2.3	-0.11	-0.12					1.14	2.35
	32	1,35	3.08	-0.12	-0.15					1.34	2.99
PEO 750 9%	50	2.3	34.3	-0.21	-0.23	-0.23	-0.26	0.77	0.73	2.3	32.2
	32	4.7	29.2	-0.22	-0.27					4.8	28.3
	26	5.9	22.9	-0.28	-0.3					5.6	22.3

750 and Carbopol. The concentrations of samples were the same as in the previous study.

It is noted that the effect of transition of the flow from the Newtonian behavior to the non-Newtonian occurs at concentration of 5%, as it was observed for PEO 750 non-thermally treated sample, but at a higher temperature, of 55° C, compared to untreated system in which the transition takes place around the temperature of 37 ° C, Figure 2.13. The values of parameters are presented in Table 2.4.

Aqueous dispersions of Carbopol

From the analysis of the results on samples of Carbopol, it is noted that these samples shows a slight decrease in viscosity after thermal treatment.

Table 2.5. Experimental and calculated values for Carbopol gel's rheological parameters, thermally and non thermally treated, with concentrations 0,5%, 1% and 1,5%.

Sample	$t\ (^0C)$	$a\ (Ns/m^2)$		n		x_{av}		x		$a^*\ (Ns/m^2)$	
		untreated	treated	untreated	treated	untreated	treated	untreated	treated	untreated	treated
Carbopol 0,5%	32	0.22	0.16	0.42	0.34	-0.63	-0.68	-0.58	-0.66	0.5	0.16
	42	0.25	0.23	0.38	0.34			-0.62	-0.66	0.55	0.23
	55	0.27	0.57	0.32	0.29			-0.68	-0.71	0.6	0.57
Carbopol 1%	26	4.84	0.84	0.26	0.15	-0.77	-0.83	-0.74	-0.85	4.81	0.84
	37	5.84	0.9	0.21	0.23			-0.79	-0.77	5.87	0.91
	55	6.58	1.09	0.20	0.15			-0.80	-0.85	6.61	1.08
Carbopol 1,5%	26	3.42	4.07	0.20	0.15	-0.78	-0.84	-0.80	-0.85	3.41	4.07
	32	3.50	4.38	0.25	0.17			-0.75	-0.83	3.47	4.32
	42	3.92	4.87	0.19	0.17			-0.81	-0.83	3.92	4.87

Carbopol gels are observed in all domains of temperature and concentration that n, x and x_{av} show a decrease in thermally-treated systems compared to non-thermally treated systems, Table 2.5.

Power exponent n decreases with increasing polymeric concentration from $n = 0.34$ to 0.5% to $n = 0.17$ to 1.5%. The samples are characterized by a non-Newtonian type of flow (shear-thinning), $n < 1$ [7, 8].

2.2. Mathematical analysis of flow curves.

As it was shown in previous results, η depends on the concentration (noted by Φ), T and $\dot{\gamma}$. These dependences were analyzed separately, without using a single equation. In this study, we are attempting to focus

their dependencies into a single expression. A first step of this exercise is to determine the E_a of the process flow.

For a broad range of viscous fluids this dependence is exponential, expressed by the equation:

$$\eta = A\exp\left(\frac{E_a}{RT}\right) \qquad (2.6.)$$

where E_a represents the activation energy of flow process at constant shear rate, A is the pre-exponential factor, T is absolute temperature and R is the universal gas constant.

Because previous results showed a dependence of viscosity Vs. shear rate, it was also tested the possibility of dependence of E_a Vs. $\dot{\gamma}$. Therefore viscosity determination was performed at different shear rates, but constant speed, respectively *50*, *100* and *150 rpm*. Regardless of shear rate for all concentrations observed linear dependence of logarithm of viscosity depending on the inverse temperature, Figure 2.22.

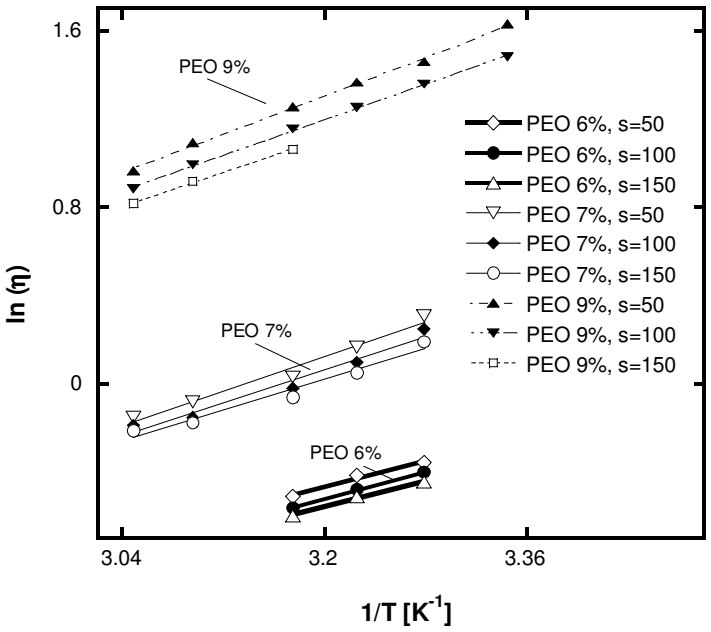

Fig. 2.22. Activation energy performed for PEO 750 gels with concentrations 6%, 7% şi 9% at shear rate 50, 100 şi 150 rot/min

Changing concentration leads only to a slight variation of these slopes, indicating a small variation of E_a depending on the concentration. This increase of activation energy with concentration can be explained by increasing number of temporary connections in the gel structure which implies a higher energy flow. This behavior indicates an Arrhenius dependence and allows calculating the activation energy from the slope of the linear representation.

To better characterize the rheological behavior of polymeric gels investigated in this study implies a mathematical analysis that combines the two models presented in the previous paragraphs.

The previous paragraphs show that both PEO gels and Carbopol aqueous dispersions presented similar changes of the viscosity depending on shear rate and settled that the best approximation of experimental data is given by power law model [17]. The equation describing this dependence is

$$\eta = a \cdot (\dot{\gamma})^{n-1} \tag{2.7}$$

Where η is viscosity, $\dot{\gamma}$ is shear rate, *n* is the exponent power.

At a constant shear rate, the term $(\dot{\gamma})^{n-1} = B = const$, becomes constant and viscosity variation is expressed only by the function of $a(T,\phi)$.

$$\eta = a(T,\phi) \cdot B \tag{2.8}$$

Typically, the temperature dependence of viscosity is expressed by the experimental law type [29]:

$$\eta = C(\phi) \cdot exp\left(\frac{E_a}{RT}\right) \cdot B \tag{2.9}$$

E_a is the flow activation energy, *R* is the universal gas constant and $C(\phi)$ is a proportionality factor, which contains contribution of

concentration. Combining equations (2.8) and (2.9) we obtain the explicit expression of the $a(T,\phi)$.

$$a(T,\phi) = C(\phi)exp\left(\frac{E_a}{RT}\right) \tag{2.10}$$

For each concentration were used the corresponding average values of E_a, in equation 2.10, in order to describe the temperature dependence of the function $a(T,\phi)$. Combining the two temperature-dependences (equation 2.10), and shear rate (equation 2.7), we can write a new equation for viscosity .

$$\eta(\phi,T,\dot{\gamma}) = C(\phi)\cdot exp\left(\frac{E_a(\phi)}{RT}\right)\cdot(\dot{\gamma})^{n-1} \tag{2.11}$$

This equation combines the dependence of viscosity on the temperature, concentration and shear rate. Using equation 2.11 we obtain a better characterization of flow curves than the results obtained by applying a power law, equation 2.5, because mathematical analysis using equation 2.11. expresses viscosity by a concentration , temperature and shear rate dependence. This result can be seen in Figure 2.28, where with

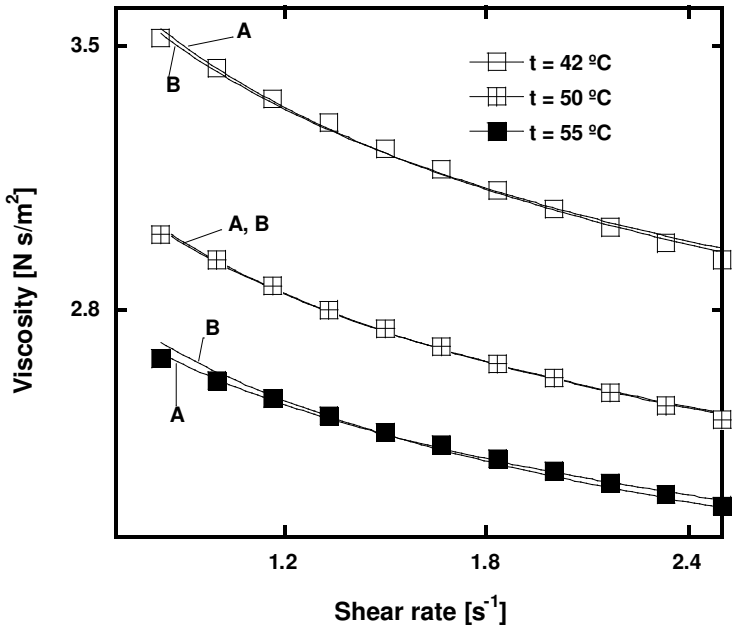

Fig. 2.28. Mathematical analyses for PEO 750 samples with 9% concentration, using Law Power equation, A curves and mathematical analyses for the same sample using 2.11 equation and B curves.

A is noted the curve resulting from the mathematical analysis based on a power law, and with B is noted curve resulting from the analysis using equation 2.11.

Good correlation between experimental and theoretical data and the fact that $C(\phi)$ is constant for all temperatures, confirms the validity of this equation for aqueous PEO gels.

2.3. Investigation of PEO polymer and Carbopol systems by electrical methods.

Measurements to determine dielectric constant were performed using Q-meter Tesla BM 409G, with frequency between 15 -300 MHz . The dielectric constant values obtained for all samples investigated were in the range 2 to 10 pF/m

Effect of concentration.

PEO aqueous gels were prepared for following concentrations 0.5%, 2% and 4%. The results show an increase of dielectric constant with increasing concentration, Figure 2.29.

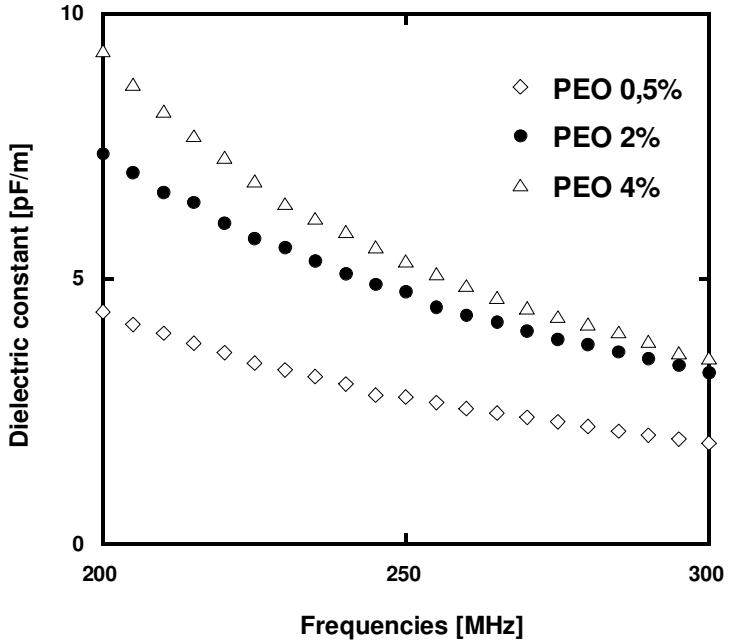

Fig. 2.29. Dielectric constant Vs. frequencies for PEO 750 gels with concentrations 0,5%, 2% and 4%.

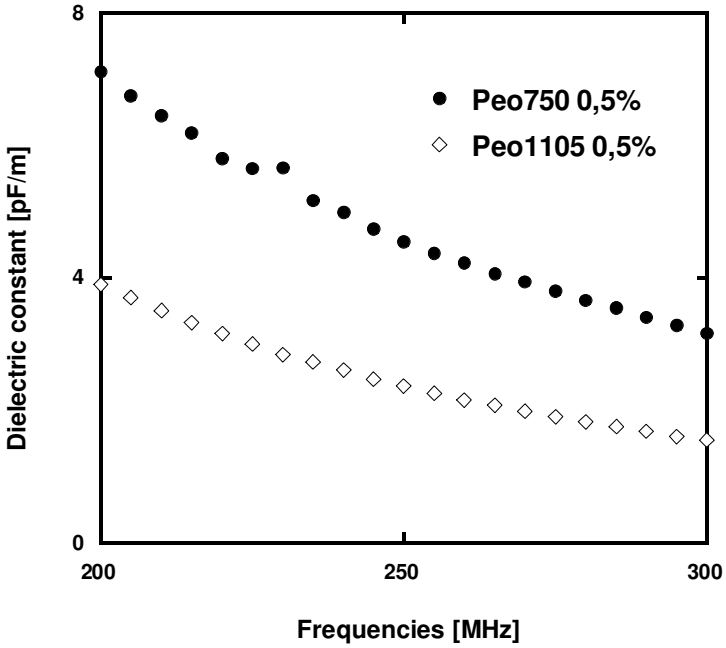

Fig. 2.31. Dielectric constant Vs. frequencies for PEO 750 and PEO 1105 gels with concentration 5%.

Effect of molecular weight

The result of this study show that dielectric constant decreases with increasing molecular weight material, Figure 2.31.

Effect of thermal treatment

Still have the same set of measurements performed for 750 samples

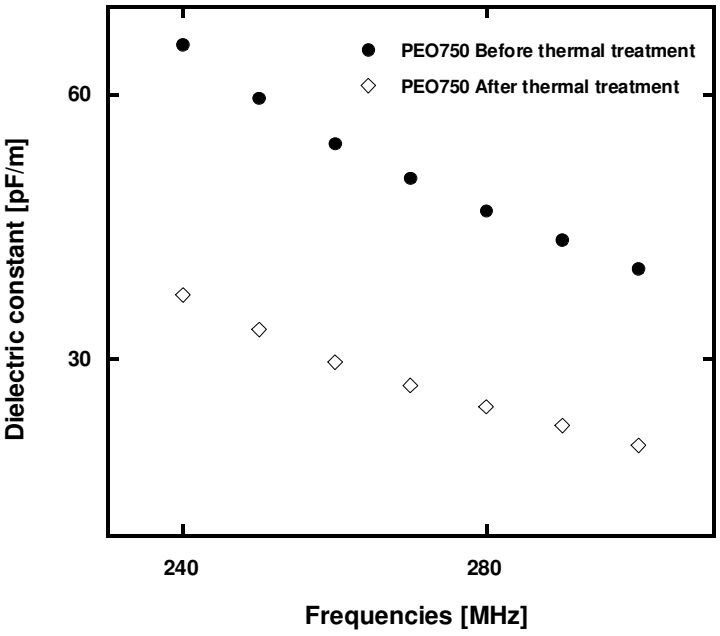

Fig. 2.32. Dielectric constant Vs. frequencies for PEO 750 gels with the same concentration 0,5%, before and after thermal treatment.

of PEO, concentration of 0.5% non-thermally treated and for thermally treated system.

After analyzing the experimental results, we observe that the dielectric constant of these systems decrease after thermal treatment, in this frequency range, Figure 3.32.

III. Vibration study performed by PEO and Carbopol matrices

The stability physical and chemical properties of polymeric materials are determined by the dynamic processes occurring at molecular and macromolecular level. These processes are strongly influenced by the action of external physical and chemical agents, repeated mechanical stress, heating-cooling cycles, the repeated action of solvents, UV action, γ, etc.

In our study we were interested by the following effects:

- Effect of molecular weight
- Solvent action
- Effect of concentration
- Effects that occur in repeated drying and rehydration processes
- The effect of γ radiation.

3.1. Materials and equipment used

Spectroscopic investigations were carried out using a confocal Raman microscope, model: R. Alpha300. Investigated samples were irradiated with a laser (He-Ne) with 633 nm wavelength and a frequency-doubled NdYAD laser wavelength 532 nm. The samples investigated were poly(ethylene oxide) PEO 750 and PEO 1105, with molecular weight 75 000 g/mol, respectively 110 500 g/mol in powder state and

polyacrylic acid Carbopol 940 and 980 with two molecular weights 104 400 g/mol, respectively 1 021 317 g/mol [4].

3.2.1. Raman spectroscopy investigation of poly(ethylene oxide) gels

Effect of molecular weight.

We investigated the samples PEO750 and PEO1105 powder with different molecular weight. Raman spectra of these samples are identical (Fig. 3.6).

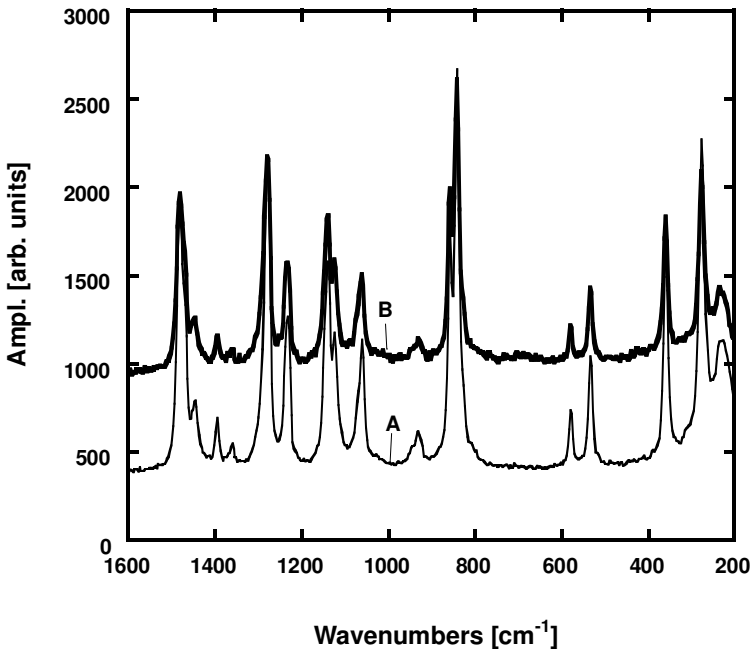

Fig. 3.6. Raman spectra of the PEO 750 (A) and PEO 1105 (B) samples in solid state.

Aqueous dispersions.

Was monitorized and compared the behavior of aqueous dispersions and of solid samples of PEO. In aqueous solution, an important change appears in the spectrum 200-600 cm^{-1} where the

spectrum is not resolved, due to the diffusion of light that occurs due the conglomeration polymer gel in areas with heterogeneous polymer concentration, which leads to Rayleigh is split, a situation common in colloidal suspensions [25]. In 1000-1500 cm^{-1} range, aqueous solution spectrum contains approximately the same vibrational modes as the solid sample spectrum, but the lines are wider, Figure 3.7.

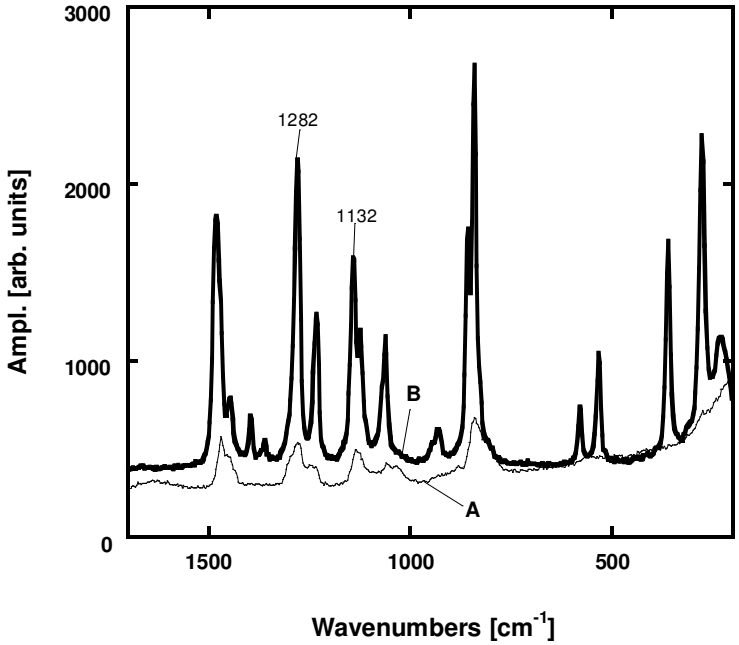

Fig. 3.7. Comparison between the Raman spectrum of PEO 750 sample in powder state (A) and disolved in water (B)

Effect of concentration

Changing the polymer concentration in this domain (5% -10%) does not change substantially the vicinity of polymeric chains. As a result, local vibrations of the chain are less affected and Raman spectra remain unchanged.

System PEO-clotrimazole

Analysis by optical microscopy indicates a colloidal suspension of clotrimazole in the polymeric matrix, the spectra obtained from regions

with different optical appearance being different. For example, curve A in Figure 3.9. is PEO gel spectrum and curve B of Fig. 3.9. is clotrimazole spectrum, included in gel.

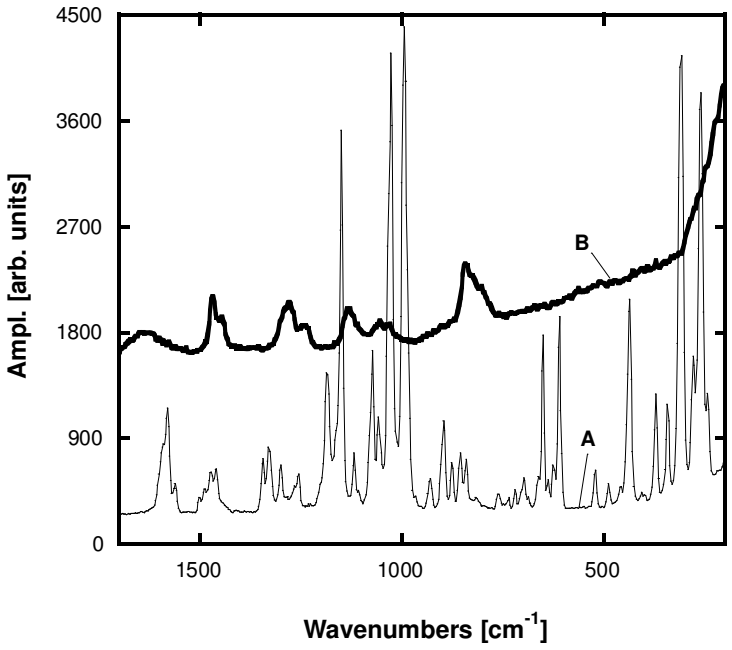

Fig. 3.9. Raman spectra of Clotrimazole (A) and PEO 750 gel (B) collected from two different areas on the sample.

On the other hand, if we compare the spectrum of pure clotrimazole powder, with the spectrum of a single clotrimazole granule included in gel, we find that they are identical. Therefore, PEO 750 matrix did not influence the specific vibrational modes of clotrimazole, Figure 3.10. Both spectra are identical. This result is very important for medical applications, as the active substance (clotrimazole) does not undergo any change in its properties when introduced into polymer matrix.

Raman spectroscopy method for investigation of clotrimazole granules can be optimized, to identify the exact area they occupy in the polymeric matrix, Raman imagery method.

Since there are no other distinct areas of interface between clotrimazole and the gel polymer, it can be said that the two distinct components of this system do not interact chemically with each other.

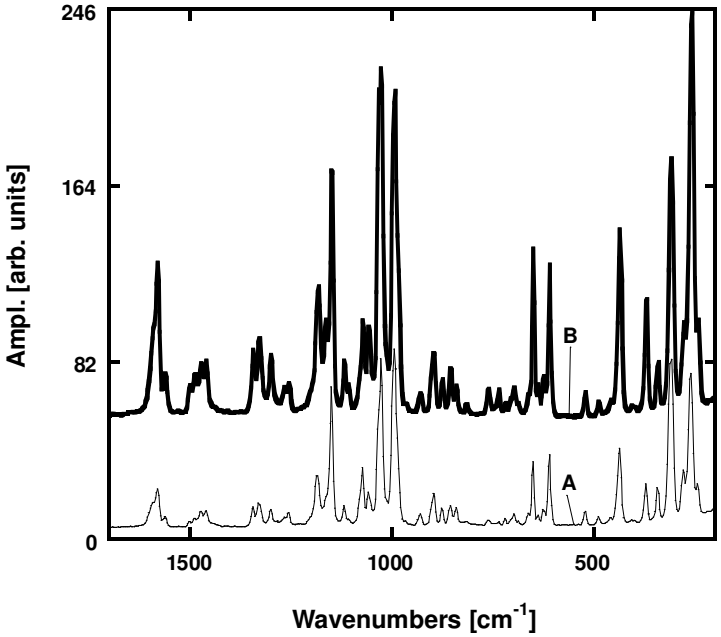

Fig. 3.10. Raman spectra of pure Clotrimazol (B) and Clotrimazol granule embedded in PEO 750 gel matrix (A).

3.2.2. Drying effect upon PEO matrix.

Experimental procedure for monitorizing the effects of repeated hydration-drying, was performed under continuous monitorizing of concentration, respectively after each drying process, water in amount of that lost during drying was added and was mixed until a homogeneous mass of polymer gel was obtained. In Figure 3.14 is shown Raman spectrum of PEO 750 gel concentration of 5% after the first drying, compared to the PEO 750 powder spectrum.

AFM technique could reveal the effect of PEO 750 concentration for dried gels and the effect of repeated hydration and drying of these gels. Increasing the concentration of PEO 750 gel's leads to an increased

surface roughness and by increasing the number of repeated hydration and drying decreases the surface roughness of these gels. Results from the AFM technique can be correlated with rheometrical measurements presented in the previous paragraphs, in order to establish an optimal recipe for a final drug product.

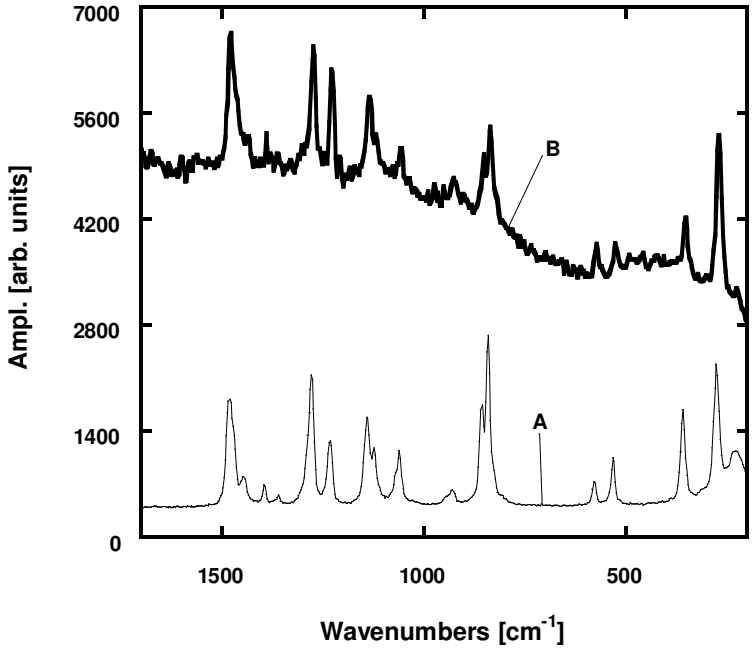

Fig. 3.14. Raman spectra of pure PEO 750 (A) and PEO 750 gels with 5% concentration after water evaporation (B).

3.2.3 Raman spectroscopy investigation of gels of Carbopol

Carbopol 940 and 980 samples with different molecular masses are characterized by similar Raman spectra (Fig. 3.20.). Therefore, it can be said that polymer's chain length and extremity movements have very little influence on local structure of the monomer [19].

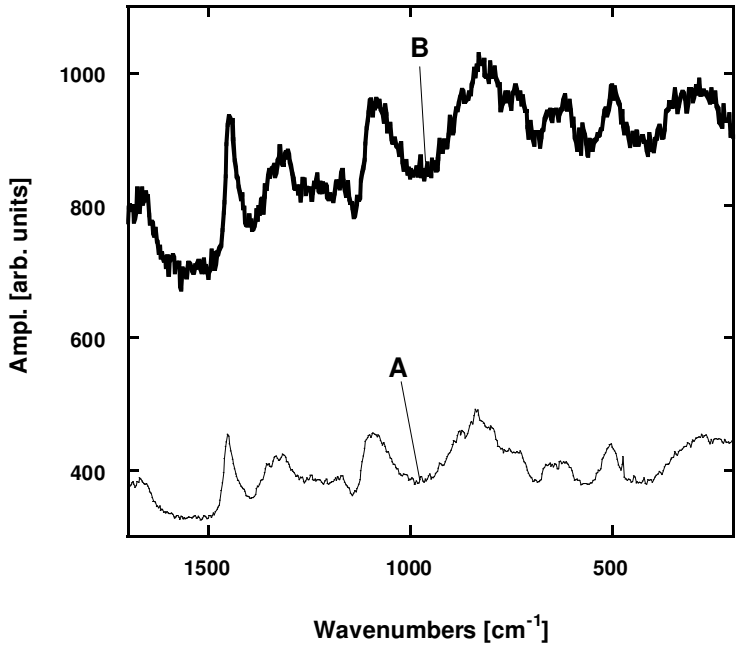

Fig. 3.20. Raman spectra of Carbopole with molecular weights (Carbopol 940, curve A and Carbopole 980, curve B).

Carbopol System - clotrimazole

In this polymeric matrix is introduced clotrimazole, achieving a colloidal suspension. Raman spectra were raised in different parts of the

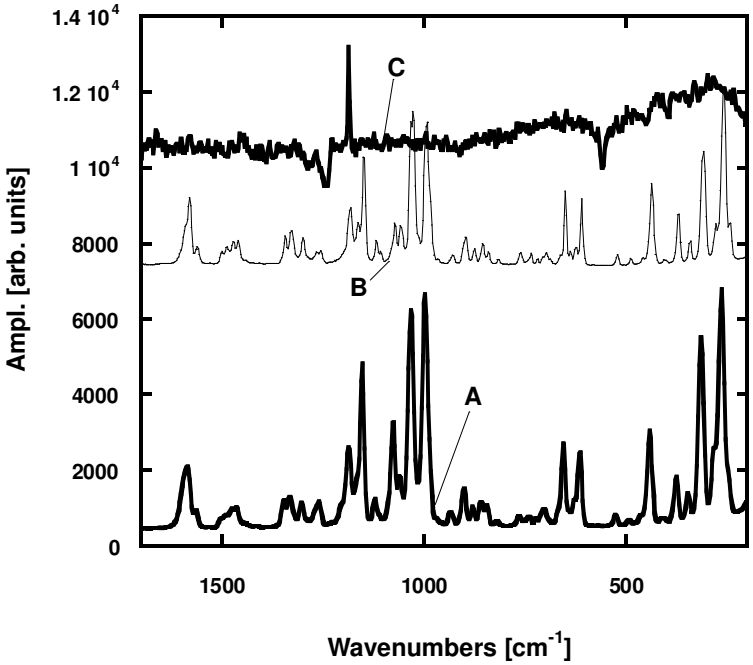

Fig. 3.23. Raman spectra of Clotrimazole samples in powder state (A) and embedded in stabilized gel (B) and the Raman spectrum of the stabilized gel (C).

stabilized gel containing clotrimazole and were compared with its pure spectrum. In some areas of the sample, Raman spectrum is broad and without a well defined structure, similar to the spectrum consisting of Carbopol 940 aqueous dispersion and water (curve C, Fig. 3.23.).

3.2.4 Drying effect upon Carbopol matrix

Next, we tried an analysis of a dry Carbopol gel by Raman imagery method. This method was used under the same conditions and were followed the same analytical steps as for PEO 750 gel. In Figure 3.25 was obtained a map representing a combination of Raman band at 1454 cm^{-1} and Carbopol gel band at 1045 cm^{-1} specific clotrimazole embedded in polymer gel, specific bands of both phases were extracted from that Raman spectrum, Figure 3.24. In Figure 3.25 the green area, noted with A we find Raman spectra of clotrimazole and red zone marked with B is a map of specific Raman spectrum of Carbopol gel.

In Figure 3.25, in the left side there is a microscopic image of the area *10x10 μm*, where the scan of the map was Raman performed .

AFM image analysis shows that the increasing concentration of polymer, Carbopol gel has a surface the dishevelment increase. This is presented like a heterogeneous form in polymeric gel, where polymer concentration is higher. Increasing polymer concentration, increases the size of the inhomogeneous domains, leading to increase the dishevelment highlighted by AFM technique.

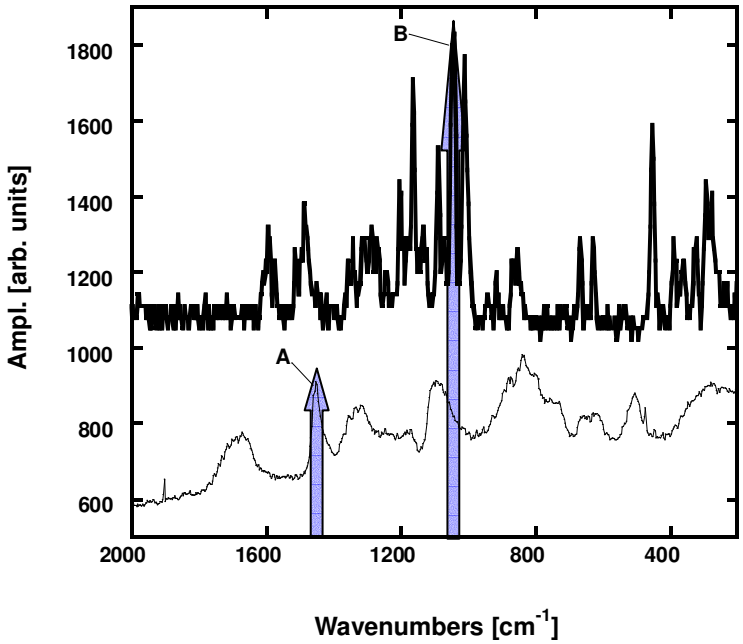

Fig. 3.24. Raman spectra collected from two specific spots on the sample.

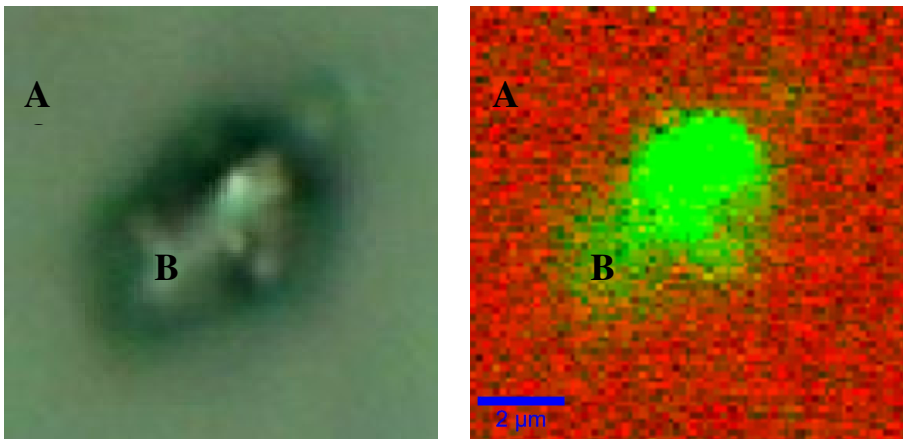

Fig. 3.25. Optical image of the sample (left) and combined Raman map obtained by reconstructing the spatial distribution of the 1450 cm^{-1} (Carbopole - zone A) and 1045 cm^{-1} (Clotrimazole - zone B) bands intensities.

3.2.5 Irradiation effect upon polymer matrix

As a source of γ radiation was used radioelement Co^{60} with a dose of 930.8 Gy on exposure.

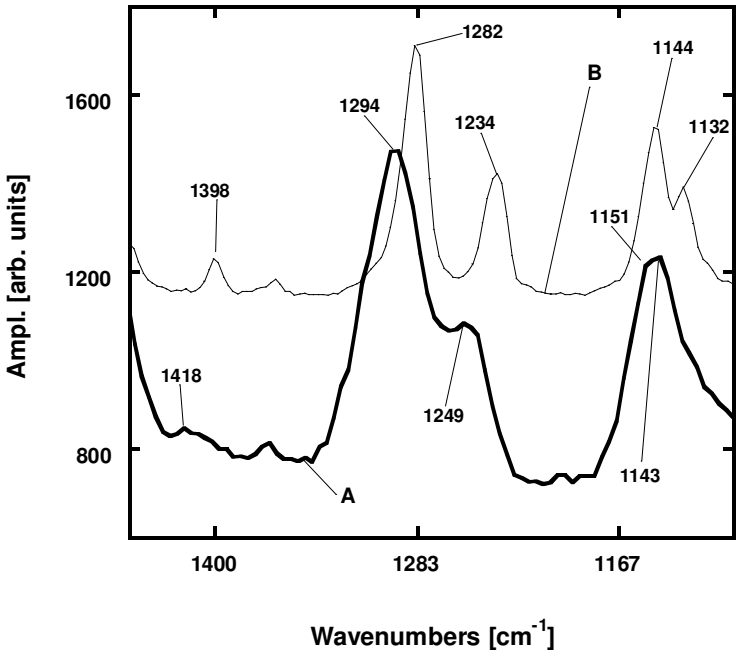

Fig. 3.29. Raman spectrum of pure, unirradiate, dry PEO 750 (curve B) and Raman spectrum of dry P0 irradiate with 930,88 Gy dose (curve A).

After irradiation of P0 gel, significant changes of vibrational modes can be observed (Fig. 3.29), particularly in range 1100-1450 cm^{-1}. For bands that are not included in this range do not appear significant changes of vibrational modes of bands.

Stretching vibration band link specific to C-O and rocking vibration band attributed to CH_2 radical at 1144 cm^{-1} after irradiation, widens. Also, specific band vibration twisting of the CH_2 group moves from 1234 to 1249 cm^{-1}. Another important shift occurs in specific vibrational mode of twisting vibration of CH_2 radical from 1282 to 1294 cm^{-1}. After sample irradiation of Carbopol 940 with γ radiation at a dose of 930.88 Gy, important changes are observed in Raman spectrum, Figure 3.30. In a careful analysis of spectra is observed that only intense band at 1105 cm^{-1} remains exactly at the same wavenumber after irradiation. This band is attributed by Dong et al, to stretching vibration of two carbon atoms of chain, which are neighbors in polyacrylic acid. Intense band at 1683 cm^{-1} disappears after irradiation, this band is attributed to stretching

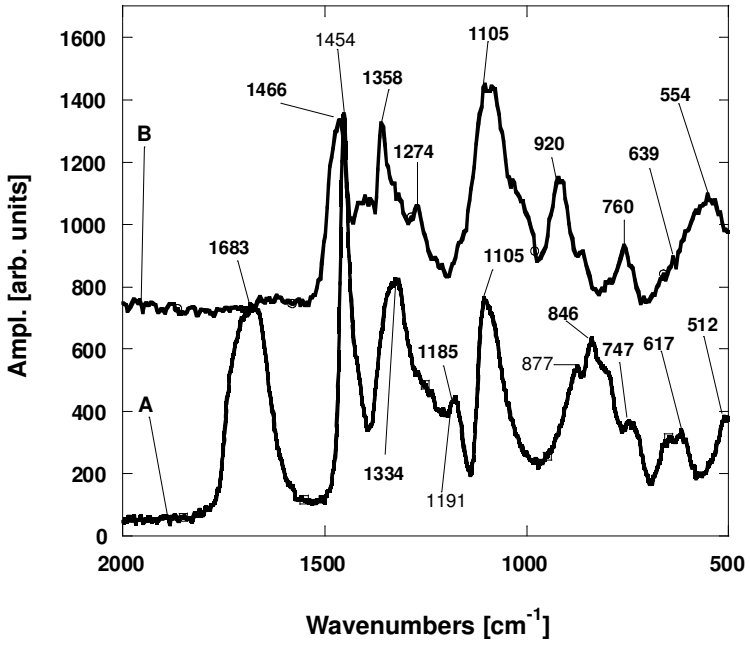

Fig. 3.30. Raman spectrum of pure, unirradiated Carbopol 940 (curve A) and Raman spectrum of Carbopol 940 after irradiation with 930,88 Gy dose.

vibration of the cross link between C = O of the carboxyl group. This band disappeared after irradiation or decreased greatly in intensity, due to destabilization of the carboxyl group.

Raman spectrum of clotrimazole, after irradiation do not show significant changes, all the bands are found in the same wavenumber, after irradiation with a dose of 814.52 Gy, Figure 3.34.

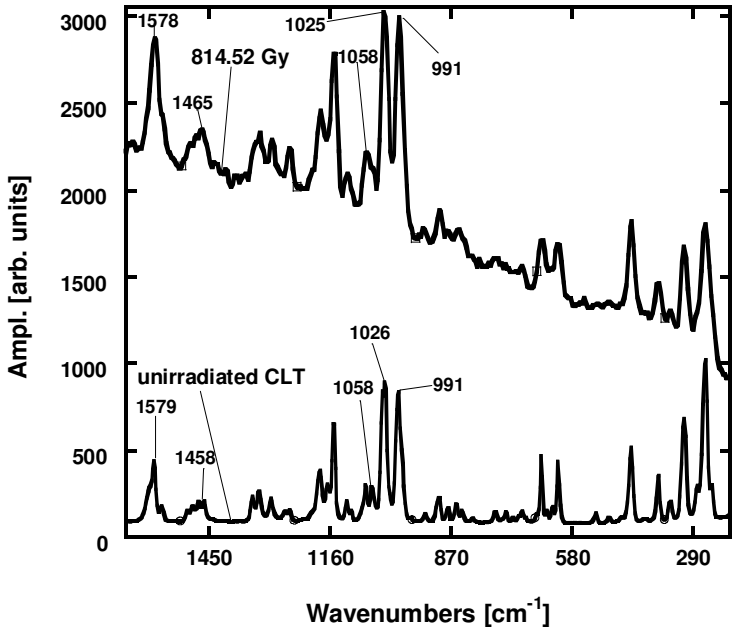

Fig. 3.34. Raman spectrum of Clt0 and Raman spectrum of pure, unirradiated Clotrimazole.

VI. General conclusions

Changes in viscosity of aqueous PEO gels non-thermally treated, depending on temperature and concentration, show a shift from non-Newtonian behavior to the Newtonian one. Polymer gel passes in first stage, from a shear-thickening flow type ($n > 1$) to Newtonian flow and then to shear-thinning flow type ($n < 1$).

Viscosity depending on temperature decrease was observed in samples thermally treated PEO 750. The transition from non-Newtonian behavior to the Newtonian one occurs at a higher temperature, at 55 ° C for samples thermally treated, and compared with 37-55 ° C untreated samples.

Carbopol samples thermally treated show a decrease of viscosity. Also, these tests highlighted an increase in viscosity with temperature and decrease in viscosity with increasing shear rate. This behavior reveals a non-Newtonian flow type shear-thinning ($n < 1$).

The results obtained by AFM technique and electrical measurements can be correlated with the rheometrical ones, presented in the previous paragraphs, in order to determine an optimum recipe for a final drug product.

A colloidal suspension is obtained by introducing clotrimazole in the PEO and Carbopol gels. Analysis by optical microscopy shows no dissolution of clotrimazole in the PEO or Carbopol gels [29]. This is confirmed by Raman spectroscopy and Raman imagery.

Raman spectrum of clotrimazole, appearing after radiation γ exposure is influenced by bands` movements, at 1460 and 1510 cm^{-1}, but this dose of irradiation does not present a significant destabilization of the molecule, but has a weak effect of ionization. However, the use of

clotrimazole in pharmaceutical applications is not recommended after prolonged exposure to γ radiation.

Polymeric matrix composed of γ Carbopol gels presents chemical instability after radiation exposure exceeding 698.16 Gy dose, as evidenced in particular by breaking the link C = O of carboxyl group and other inherent changes that occur in the polymeric chain due to this split.

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