SYNTHESIS AND CHARACTERIZATION OF HYDROGELS COMPOSED BY DIFFERENT TYPES OF POLY(VINYL ALCOHOL)

Alcântara, Mara Tânia Silva[1]; Varca, Gustavo Henrique Costa[1] ;Amaral, Renata Hage[1]; Mattos[1], Thamires Cristinne B; Riella, Humberto Gracher.; Lugão, Ademar Benévolo.
[1]Instituto de Pesquisas Energéticas e Nucleares IPEN – CNEN/SP, Brasil
E-mail: maratalcantara@uol.com.br

Abstract. *PVA is a synthetic water-soluble, biodegradable and biocompatible polymer. It is widely used in pharmaceutical and biomedical applications for controlled drug release. The basic properties of PVA are known to depend upon the degree of polymerization and on the degree of hydrolysis as well. Thus, the aim of this study was to develop a hydrogel with improved mechanical properties and also evaluate the influence of the different PVAs in the hydrogels properties in order to assess their potential application in matrices for advanced controlled drug release systems. The hydrogels were synthesized with agar, carrageen and PVAs holding different hydrolysis (88 and 98 %) rates and molecular weight using gamma radiation from ^{60}Co source in order to promote an adequate crosslinking and sterilization simultaneously. The properties of the hydrogels formed were determined by the analysis of the swelling ratio, gel content and mechanical properties. The results indicated the matrices composed by partially hydrolyzed grade PVA presented enhanced mechanical properties and crosslinking over the fully hydrolyzed grade. The properties of the PVA used for the preparation of the evaluated hydrogels conferred different properties to the hydrogels and the molar mass played an important role in the crosslinking process of fully hydrolyzed PVA grades.*

Key Word: *Hydrogel, PVA, Polymeric matrices*

1. INTRODUCTION

Hydrogels are known to present crosslinked polymer network structures composed of hydrophilic polymers, which are insoluble and also hold the ability to absorb high water content [Byrne et al, 2002].

Synthetic hydrogels are being explored in the pharmaceutical field due to their compatibility with organic tissues [Trieu et al, 1995] which is attributed to the high water content as well as its physical surface properties [ITOI et al, 1965].

Different kinds of hydrogels are currently employed in a variety of medical applications such as (i) topical applications, as wound dressings; (ii) drug-delivery systems; (iii) transdermal systems; (iv) dental applications; (v) injectable polymers; (vi) implants; (vii) ophthalmic applications; and (viii) stimuli-responsive systems [Trieu et al, 1995].

Regarding controlled release systems this particular pharmaceutical form has been proposed as a matrix for the release of bioactive compounds, like antibiotics, anticancer, enzymes, contraceptives, ophthalmic preparations and antibodies among others [Ranade et al, 2003].

A drug release system is a term referred to the technology applied to optimize the release of a drug, where it must be time-released or absorbed, which leads to a better therapeutic response [ANSEL et al, 1999]. The maintenance of therapeutically optimum drug plasma concentrations through zero-order release without significant fluctuations and elimination of the need for frequent single dose administrations represent the two main advantages of controlled drug delivery systems [Ranade, 1991].

Hydrogels composed by PVA correspond to one of the most widely studied and applied release systems due to their biocompatibility and low reactivity with the loaded drugs [Keita et al, 1990]. Besides such characteristics, these products hold excellent mechanical properties and are biodegradable under determined conditions [Wang et al, 2004].

The hydrogel drug release relies upon the degree of crosslinking [Keita et al, 1990] and the structure of the polymeric net.

The commercially available PVA is a mixture of different stereochemical structures (isostatic, sindiotatic and atatic). The stereochemistry and the physico-chemical properties are highly dependent upon the preparation methods [Wang et al, 2004] and the crosslinking levels, which lead to a tridimensional net able to absorb high water content and thus forming a hydrogel.

Synthetic and natural polymers may be combined with polysaccharides such as agar and carrageenan in order to produce hydrogels. Carrageenan is mainly used in the food industry as a gelling, thickening and stabilizing agent [Tye, 1989]. When added to hydrogels it is able to increase the swelling equilibrium in the pharmaceutical form [Dafader et al, 2009].

There are different physical and chemical methods that may be applied in order to form the bonds between the hidrogel structures. The chemical methods provide covalent attachments which are present in the polymeric chains. However, such agents are frequently toxic and need to be removed from the gel prior to its usage [Hennink et al, 2002].

Polymer irradiation is an important process in the hydrogel synthesis and modification of polymeric materials used in the immobilization of bioactive substances, which constitute drug release systems [Carenza, 1988]. The Synthesis of hydrogels using radiation offers special advantages, not only due to the achieved strong interaction between chains through covalent bonds, but it also solves the problem of sterilization, and allows the fabrication of pure non-contaminated products with residuals of toxic compounds [El-Din et al, 2007].

The ability of ionizing radiation to kill microorganisms was established in the past century [Dorpema et al, 1990]. The ^{60}Co radiation sterilization consists of a simple, rapid and effective process and its beneficial effects were further supported by the knowledge that gamma radiation provides a cost-effective mode for sterilization of biomedical materials and devices. [Benson et al, 2002]. The standardized dose used to sterilize medical devices is 25 kGy [Dorpema et al, 1990].

The specific properties of a polyvinyl alcohol such as 1,2-glycol content, tacticity, branching, average length and distribution of residual acetyl group sequences, especially in partially hydrolysed grades, provide an individual property profile for each PVA [Mowiol brochure, 1999]. It is clear that these particular PVA properties lead to specific hydrogel characteristics. Thus, the aim of this study was to evaluate the properties of hydrogels prepared with different degree of hydrolysis and molecular weight of the PVAs.

2. MATERIALS AND METHODS

2.1 Materials

Fully hydrolysed PVA grades and partially hydrolysed PVA grades were acquired from Clariant and Dermet Agekem; Natural polysaccharides agar-agar (agar n° 1) was from Oxoid and kappa carrageenan (KC) from Agargel.

Table 1. Relationship between the hydrogels synthesized, molar weight and properties of the PVAs used

Hydrogel	$\bar{M}w$ (g/mol)	Degree of hydrolysis (%)
A	81,000	98 - 98,8 (fully hydrolysed grade)
B	31,000	
C	160,000	86,7 - 88,7 (partially hydrolysed grade)
D	120,000	87- 89

2.2 Preparation of Hydrogels

The hydrogels were prepared by mixing PVA (10% w/w), agar (0,6% w/w), KC (0,6 % w/w) and reverse osmosis water. The mix was heated at 120°C, 1Kgf/cm2 for 15 minutes in autoclave. The solutions were then poured in plastic mould, sealed and irradiated with gamma rays generated from a ^{60}Co. The dosage used used was 25 kGy for hydrogels A, C and D, and 50 kGy for hydrogel B. The hydrogels were irradiated at 1,98kGy/h.

2.4 Characterization

2.4.1 Gel fraction

The concentration of the cross-linked material, forming the insoluble fraction, was estimated using ASTM D 2765-01 with some modifications. The Hydrogels were packaged in stainless steel 500 mesh porous bag. After dried in stove at 60°C until a constant weight was reached, the sample was submitted to extraction using a soxhlet and distilled water as solvent. After 40h the bags were dried and re-weighed until constant weight was reached. The gel fraction was calculated as Eq.(1), using the initial weight of the dry gel (W_i) and the weight of the extracted dry gel (W_d). The gel fraction estimated corresponded to the average of data of 3 analyzed specimens of each formulation.

$$\text{Gel}(\%) = \frac{\text{Wd}}{\text{Wi}} \text{x} 100 \quad (1)$$

2.4.2 Swelling

Reverse Osmosis Water was used for the investigation of swelling properties of the hydrogels at room temperature. At a given time, each specimen was removed from the water to be sieved where it was carefully wiped by filter papers and then weighted. This procedure was repeated several times up to 48h. The swelling percentage of hydrogels was calculated based on Eq. (2), which consists of the difference between the initial and the final weight of the sample divided by the initial weight. Where: Ws corresponds to the weight of the swollen gels and Wd to the gel weight before immersion. Tree samples of each formulation were analyzed in order to estimate the swelling capacity of the hydrogel.

$$\text{Swelling}(\%) = \frac{\text{Ws - Wd}}{\text{Wd}} \text{x} 100 \quad (2)$$

2.4.3 Mechanical properties

A Stable Micro System, model TA.XT plus, texture analyzer equipped with a 50Kg load cell was used to measure the strain and stretched of the hydrogels. The tensile strength of hydrogels were examined by ASTM D 638-03, however the stress and strain (%) at break of hydrogels were measured using rectangular specimens measuring of 24 x 100mm.

The stress was calculated based on the cross-section area of each sample and the strain based on its relative elongation in percentage from its original length (lo = 60mm). The matrices were stretched at a strain rate of 8.33mm.s $^{-1}$ for the samples A, C and D. Sample B was stretched at a rate of 4.16mm.s $^{-1}$, as recommended by the currents standards. The pre-test speed adopted was 2.0mm.s^{-1} and the trigger force was set to 5g.

3. RESULTS AND DISCUSSION

3.1 Gel fraction

The Network gel fractions were calculated and the results are presented in Table 2 for the hydrogels irradiated at 25kGy. Regarding partially hydrolyzed PVA (samples C and D) the different molar mass does not seem to play an important role in the crosslinking process once the results indicated a very similar crosslinking profile (Table 2). Such fact was not observed for the fully hydrolyzed PVAs (Table 2) considering that the hydrogel samples A and B presented a completely different crosslinking profile also indicating that higher mass molar PVAs led to better crosslinking.

The hydrogel composed by fully hydrolyzed PVAs grade was only formed when exposed to a radiation dose of 25kGy for the higher molar mass PVA (hydrogel A, Table 2). No crosslinking was indicated by the methodology used for the sample B, which was composed by the lower mass molar PVA. However the same hydrogel (Sample B) did present crosslinking of 54.9 ± 2.1% when the irradiated dose was doubled to 50kGy.

Table 2 – Gel fraction of PVP/Agar/KC hydrogels crosslinked using 25kGy synthesized with PVAs holding different degree of hydrolysis and molar mass

Hydrogel	**A**	**B**	**C**	**D**
Gel fraction (%)	59.3 ± 2.9	0.0 ± 0.0	76.3 ± 0.9	74.8 ± 1.0

The differences between gel fractions of hydrogels are shown in Fig. 1. The gel fraction of sample B was not possible to measure by this method, but it was close to zero. When comparing the hydrogel A (fully hydrolyzed PVA grade) and C (partially hydrolyzed PVA grade), it's possible to note that considering the difference in their molar mass of around 100%, that the gel fraction is 17% higher, indicating that the degree of hydrolysis did influence in the crosslinking process of the hydrogel.

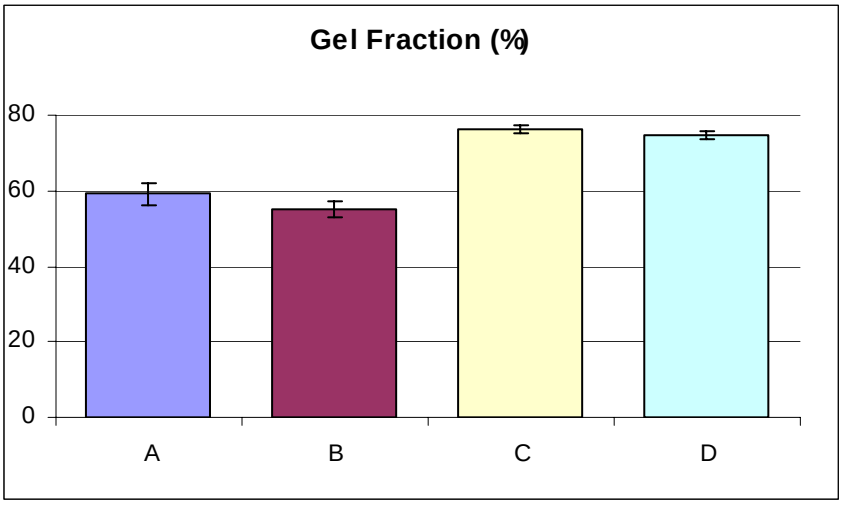

Figure 1. Variation of gel fraction of hydrogels prepared with different type of PVA, being A, C and D cross linked with 25kGy and B with 50kGy

3.2 Swelling

Considering the result that the hydrogel B irradiated at 25kGy presented no crosslinking, the measurement of the swelling capacity was only possible when such sample was exposed to a 50kGy dose. The water absorption curves are presented in Figure 2.

Relevant differences between the hydrogel formulations prepared with PVAs holding different hydrolysis degrees and molar mass were observed.

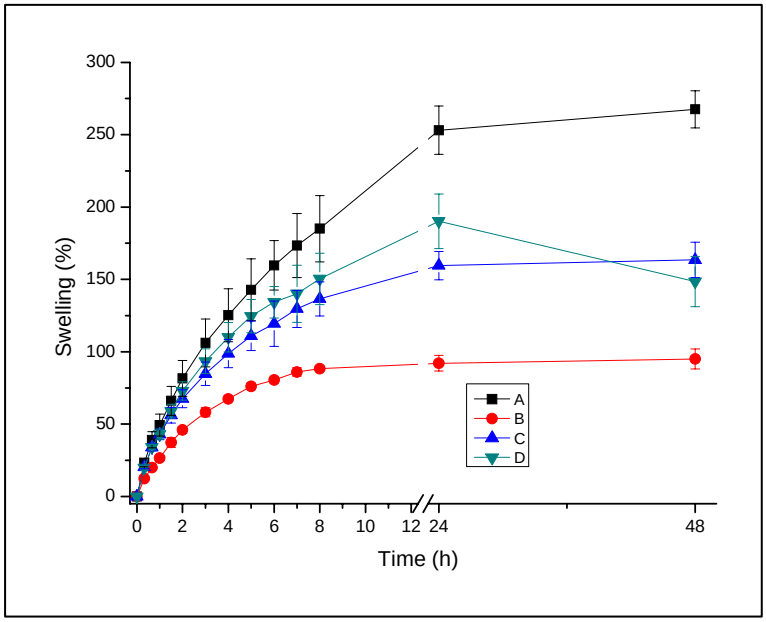

Figure 2. Swelling capacity of the hydrogels prepared. Samples A, C and D were irradiated at the dose 25kGy and B at 50kGy

The hydrogels A and B (fully hydrolyzed PVAs grade) presented the highest and the lowest swelling ability, which both corresponded to 253% and 92% respectively, after 24h immersed in water. The hydrogels (partially hydrolyzed PVAs grade) showed intermediate

swelling ability of 160% and 190% for the hydrogels C and D respectively, after the same 24 h immersed in water.

The degree of crystallization in a polyvinyl alcohol holds a major influence on the solubility and swelling ability of PVAs, but this particular effect is less pronounced in polyvinyl alcohols which do contain acetyl groups in their polymeric structure (Sample C and D) [Mowiol brochure, 1999]. Based on such information, for fully hydrolyzed PVAs grade used in hydrogels A and B, the swelling data suggests a larger crystalline structure for the hydrogel B, and a smaller crystalline structure for the hydrogel A.

Also the hydrogel B presented a higher swelling stability profile than sample A, considering that it does not suffer significant changes after 8h test (Fig. 2).

The results observed for hydrogels C and D, composed by partially hydrolyzed PVA grades and with different molar mass showed a small difference in the swelling ability between them up to 8h. After this period this difference increases slightly until a 24h period was reached. This profile was reversed after 24h suggesting that collapses may have taken place among the polymeric chains of the prepared PVA hydrogel with higher molar mass. Sample D presented a water loss between 24h and 48h immersed in water.

3.3 Mechanical properties

Under normal conditions PVA films, especially those of higher viscosity grades have a high tensile strength and good elongation at break. When shifting from low to high-molecular PVA the attractive force and tear strength do increase. This can be taken as a sign that the orientation tendency of the chains for the fully hydrolyzed PVA grades is more pronounced [Mowiol brochure, 1999] and this can be seen in Fig. 3 and Fig. 4.

The hydrogels composed by fully hydrolyzed PVA grades showed a large increase in tensile strength with PVA of large molar mass indicating the influence of molar mass on the attractive force, whereas nearly no differentiation of values is observed for the hydrogels composed by fully hydrolysed PVA grades.

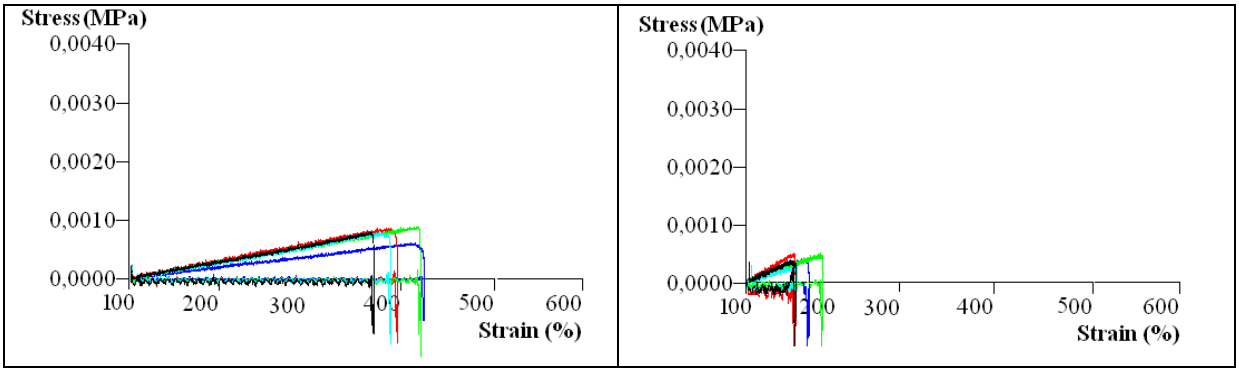

Figure 3. Tensile strength of hydrogels A and B prepared with fully hydrolysed PVA grades and irradiated at the dose of 25 kGy and 50kGy respectively

The influence of PVA in tensile properties is attributed to the fact that PVA is a semicrystalline polymer, and thus being its degree of crystallinity influences among other properties, in the tensile modulus [Mark, 1988].

The results highlighted the crystalline differences among the of PVAs used in hydrogels A and B, which if associated with the differences in molar mass explain the low strain observed for hydrogel B.

The results showed similar results of stress for the hydrogels composed by PVA with degree of hydrolysis about 88% as observed in Fig. 4.

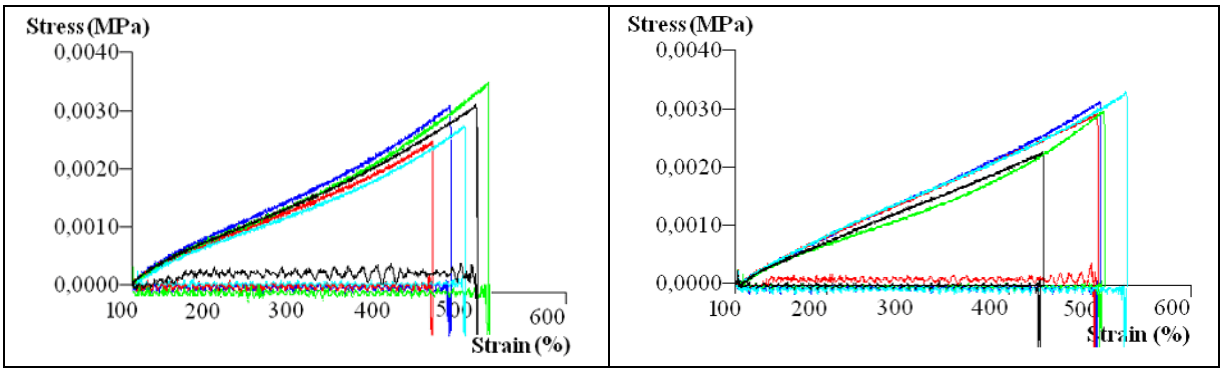

Figure 4. The tensile strength of hydrogels C and D prepared with PVA partially hydrolyzed grade crosslinked at the dose of 25 kGy

The average data obtained for the tensile strength, stress and maximum strain are very close. The rupture and elastic module of the hydrogels A, C and D (irradiated at 25kGy and hydrogel B at 50kGy) are presented in Table. 3.

Table 3 – Data obtained in analyze of mechanical properties of PVP/agar/KC hydrogels synthesized with PVA of different degree of hydrolysis and molar mass, where F = force σ_R = Tensile stress in rupture and ε_R = Strain in rupture, E= Elastic Module

Hydrogels	***F*** **(N)**	σ_R **(MPa.)**	ε_R **(%)**	***E*** **(Mpa)**
A	0.53 ± 0.03	0.0007 ± 0.0001	291 ± 21.9	1,25
B	0.19 ± 0.06	0.0003 ± 0.0001	59 ± 14,8	0,63
C	1.80 ± 0.32	0.0028 ± 0.0004	368 ± 24,1	1,32
D	2.20 ± 0.31	0.0032 ± 0.0004	389 ± 34,0	1,33

The results shown in Table 3 indicated that hydrogel A may be stretched around 291% of its original length before breaking, unlike the hydrogels C and D which may be stretched up to until 368% and 389% while hydrogel B did not hold any strength resistance.

The elastic modulus of hydrogels studied presented low values like elastomers, indicating their similarity with those materials.

4. CONCLUSIONS

The properties of the PVA used for the preparation of the evaluated hydrogels conferred different properties to the hydrogels, which highlighted the importance of a selection of an adequate PVA type according to the desirable characteristics of the polymeric matrix to be developed.

The molar mass plays an important role in the crosslinking process of fully hydrolyzed PVA grades and these particular polymers, with low molar mass, may form membranes using dosages higher than 25kGy. However a decrease in the mechanical properties is expected and such information must be considered depending on the product application.

ACKNOWLEDGEMENTS

The authors would like to acknowledge Jose Roberto Rogero, Sizue O. Rogero, Elisabeth R.S. Somessari and Carlos G. da Silveira for their contribution to the work, and the financial support given by CAPES (process PE 022/2008) and CNPq/PIBIC .

REFERENCES

ANSEL, H.C.; POPOVIVICH, N.G. (1999) Farmacotécnica: formas farmacêuticas e sistemas de liberação de fármacos. São Paulo: Editora Premier

ASTM D 882-95: Standard test method for tensile properties of thin plastic sheeting. *American Society for testing and materials*, 1995

ASTM D 570: Test Method of Test Water Absorption of Plastics, American Society for testing and materials**,** 1998

ASTM D 2765-01: Standard Test Methods for Determination of Gel Content and Swell Ratio of Crosslinked Ethylene Plastics. American Society for testing and materials, 2001.

Benson, R. S. (2002) "Use of radiation in biomaterials science". Nuclear Instruments and Methods in Physics Research, B, 191, 752–757

Byrne, M.; Parka, K.; Pepas, N.A. (2002) "Molecular imprinting within hydrogels" *Advanced Drug Delivery Reviews*, 54, 1, 149–161.

Carenza, M. (1988) "Recent Concepts of Radiation Processing" *Radiat . Phys. Chem* **. ,** 31, 887-896.

Dafader, N.C; Ganguli, S.; Sattar, M.A.; Haque, M.E.; Akhtar, F. *(2009)* "Blend Hydrogel by Gamma Radiation" .*Malaysian Polymer Journal,. 4,.2, 37-45,*

Dorpema, J.W. (1990) "Review and state of the art on radiation sterilization of medical devices".. *Int. J. Radiat. Appl. Instrum..Part C. Radiat. Phys. Chem.,* 35, I-3, 357-360.

El-Din, H.M. N.; Alla, S.G. A.; El-Naggar, A.W.M. (2007) "Radiation Synthesis and Characterization of Hydrogels Composed of Poly(vinyl alcohol) and Acrylamide Mixtures" Journal of Macromolecular Science w, Part A: Pure and Applied Chemistry 44, 47–54

Hennink, W.E; Van Nostrum, C. F.(2002) "Novel crosslinking methods to design hydrogels" *Advanced Drug Delivery Reviews*,54, 13-36.

Itoi, M.; Akiyama, T.; Komatsu, S.; Niwa, Y. (1965) "Experimental study of elastic keratoprosthesis: A preliminary report", *J. Ophthalmoogy,* 9, 146.

Keita, G.; Ricard, A. (1990) "Continuos swelling or collapse of chemically crosslinked gel of poly(vinyl alcohol) by borate complexation" *Polymer Bulletin,*24, 627-32.

Mark, H.F.; Bikales, N. M.; Overberger, C. G.; Menges, G.; Kroschwits Marten, F.L. (1988) "Vinyl Alcohol Polymers". *Encyclopedia of Polymer Science and Engineering***.** John Wiley & Sons. New York.

Mowiol brochure (1999), Clariant GmbH, Division CP - BU Polyvinyl Alcohol/Polyvinyl Butyral. Research at http://www.kuraray-am.com/pvoh-pvb/downloads/Mowiol_brochure_en_KSE.pdf in /16/04/10.

Ranade, V.; Hollinger, M. A (2003) Drug Delivery Systems. 2.ed. London: CRC Press,

Ranade, V., (1991) **"**Drug delivery systems 5A. Oral drug delivery**"** *J Clin Pharmacol.*; 31, 2-16

Trieu, H.; Qutubuddin, S. (1995) “Poly(vinyl alcohol) hydrogels: Effects of processing parameters on structure and properties” Polymer Bulletin **,** 36,13, 2531-2539.

Trieu, H.; Qutubuddin, S. (1995) “Poly(vinyl alcohol) hydrogels: Effects of processing parameters on struture and proprerties. *Polymer Bulletin,* 36, 3, 2531-9.

Tye, R. J. (1989). “Industrial and non-food uses of carrageenan” *Carbohydrate Polymer.* 10, 259 - 280.

Wang, T.; Turhan, M.; and Gunasekaran, S. (2004) “Selected properties of pH-sensitive, biodegradable chitosan–poly(vinyl alcohol) hydrogel” *Polymer Internacional***,** 53, 911-918.