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Review Article

HYDROGEL DRUG DELIVERY SYSTEM

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ABSTRACT

The dissolution of a hydrophilic polymer in water can be prevented by adding cross-links via either a physical or a chemical process. A cross-linked hydrosol is called a hydrogel and swells in the surrounding liquid to a certain swelling ratio, depending on the number of cross-links, i.e., the cross-linking density. These hydrogels have many advantageous features including, stimuli responsive, good diffusion properties, low toxicity and good compatibility, Because of their chemical structures are similar to those of the bioactive Glycosoaminoglycan (GAG) molecules present in the extra-cellular matrix. Hydrogel preparation by freeze- thaw method involves physical cross-linking due to crystallite formation. This method does not require the presence of a cross-linking agent such physically cross-linked materials also exhibit higher mechanical strength than chemical or irradiative techniques. In Physical hydrogels, mechanical load can be distributed along the crystallites of the three dimensional structures. Extent crosslinking hydrogel analyzed by FTIR and DSC. The molecular transport phenomenon, as studied by the dynamic swelling experiments.

Keywords: Hydrogel, Freeze-Thaw method, Crystallites, Swelling, Drug delivery system, FTIR, DSC.

INTRODUCTION

Every drug molecule needs a delivery system to carry the drug to site of action upon administration to the patient. Delivery of the drugs can be achieved using various types of dosage forms including tablets, capsules etc. Most of these conventional drug delivery systems are known to provide release of the drug with little or no control over delivery rate. Hydrogel drug delivery system in a simple binary system of a polymer and a liquid, a sol is formed when the polymer- liquid interaction are more favored than both polymer- polymer and liquid – liquid interactions. If the polymer is hydrophilic and liquid is water, the product of the polymer- liquid interaction is called a Hydrosol. The dissolution of a hydrophilic polymer in water can be prevented by adding cross-links. Hydrogel can only swell in surrounding liquid to a certain swelling ratio, depending on the number of cross-links, i.e. the cross-linking density. Hydrogel have many advantageous features including, low toxicity and good biocompatibility, because their chemical structures are similar to those of the bioactive glycosoaminoglycan (GAG) molecules (e.g heparin sulfate, chondrotin sulfate and hyaluonan) present in the native extracellular matrix.[8,17,21,20]

Physical and Chemical Gels

In physical gels, the nature of the cross-linking is physical process. This is normally achieved via utilizing physical process such as association, aggregation, crystallization, complexation, and hydrogen bonding. Physical networks have transient junction arising from polymer chain entanglement or physical interactions, hydrogen bonds or hydrophobic interactions On the contrary, a chemical process, i.e. chemical covalent cross-linking is utilized to prepare a chemical hydrogel. Physical hydrogel are reversible due to conformational changes

chemical hydrogels are permanent and irreversible as a result of configuration. The hydrogel will be available as a drug reservoir; loaded drugs will be released by diffusion from the hydrogels or by erosion of the hydrogel. Water inside the hydrogel allows free diffusion of the some molecules, while the polymer serves as a matrix to hold water together. The network structure of hydrogel can be characterized by a number of parameters. One parameter of particular concerns to this work is the mesh size. The mesh size is the term used to define the distance between cross-links in hydrogel network. The Change in mesh size alters the diffusion of a therapeutic moiety (proteins) from a hydrogel carrier. The releasing mechanism can be controlled by swelling or erosion of the hydrogels. The major mechanism in the erosion is very complex because it depends on the degradation, swelling, dissolution, or diffusion of oligomer and monomer residues. When a in cross-linked, amorphous, glassy polymer is brought into contact with thermodynamically compatible solvent, the latter dissociates into polymer, and when the solvent concentration in the swollen polymer reaches a critical value, chain disentanglement begins to dominate and the polymer is eventually dissolved. On the basis of this idea, polymer swelling due, to solvent penetration, and relaxation- controlled polymer dissolution kinetics had been proposed. The dissolution flux was expressed as the difference between the polymer stress gradient and the solvent osmotic pressure gradient.The dissolution process can be understood as the transformation undergone by the polymer from on entangled gel-like phase to a disentangled liquid solution. The dynamics of these polymer chains have been discussed by means of the reputation idea and the release is executed during this process and the release behavior would be affected by the property of the hydrogel because there can be diverse interactions between the hydrogel and drug. Hydrogel show minimal tendency to adsorb proteins from body fluids because of their low interfacial tension. Many hydrogels provide inert surfaces that prevent nonspecific adsorption of proteins. Further, the ability of molecules of different sizes to diffuse into (drug loading) and out (hydrogel).Hydrogels allows to possible use in drug delivery systems. Many, polypeptide drugs example insulin, are difficult to dissolve in aqueous medium under physiological condition, due to their hydrophobic character. Numerous designs and materials for the successful delivery of hydrophobic polypeptide drug had been reported. Hydrogel posses a hydrophobic domain, which is suitable for adopting hydrophobic drug such as insulin. This hydrogel showed unique erosion behavior depending on the p^H condition the hydrogel remains stable under acidic p^H condition but to formation of the hydrogen bonds. On the other hand, the hydrogel showed spontaneous erosion behavior under a neutral p^H condition, due to breakage of the hydrogen bonds by the ionization procedure of carboxyl group. The p^H dependence would be available for oral polypeptide drug carrier, protecting under acidic p^H conditions (stomach) and neutral p^H conditions (small intestine).[1,3,5,14,15,16,]

Hydrogel Oral Drug Delivery System

Eudragit, the most prominent acrylic acid based enteric coating and numerous types have been developed for specific applications. Variation in the small intestine can be exploited to target breakdown of the enteric coating to a specific region of the GI tract as discussed above. Eudragit as aqueous, anionic polymer composed of methacrylic acid and methacrylates. The exact composition can be varied target breakdown of the coatings at a specific p^H. p^H sensitive drug delivery system developed for protein- peptide drug delivery, colon targeted drug delivery, for foul tasted drugs. At low p^H (~2) protection of drug in at low p^H environment → Complexation of carrier occurs due to hydrogen bonding between polymer chains → Release of the drug in upper small intestine → Decomplexation and increase in mesh size occurs due to ionic repulsion and swelling of the polymer at high pH.

Properties of p^H Sensitive Hydrogels

Hydrogels made up of cross-linked polyelectrolytes display big difference in swelling

properties depending on the ph of the environment. The pendant acidic or basic groups on polyelectrolytes undergo ionization like acidic or basic groups of monoacids or monobases, ionization of polyelectrolytes, however, is more difficult due to electrostatic effects exerted by other adjacent ionized groups. This tends to make the apparent dissociation constant (Ka) Different from that of the corresponding monoacid or monobase. The presence of ionizable groups on polymer chains in swelling of the hydrogels much beyond that can achievable by non- electrolytes polymer hydrogels, the presence of ionizable groups on polymer chain results in swelling of the hydrogels. Since the swelling of polyelectrolyte hydrogels is mainly due to electrostatic repulsion such as p^H, ionic strength, type of counter ions. The swelling and p^H responsiveness of polyelectrolyte hydrogels can be adjusted by using neutral co-monomers, such 2-hydroethyl methacrylate, methyl methacrylate and maleic anhydride.[6,12,18]

Applications of the Ph Sensitive Hydrogels

p^H sensitive hydrogels have been most frequently used to develop controlled release formulations for oral administration. The p^H in the stomach (<3) is quite different from the neutral p^H in intestine and such a difference is large enough to elicit p^H dependent behavior of polyelectrolyte hydrogels. For polycationic hydrogels, the swelling is minimal at neutral p^H. This property has been used to prevent release of foul tasting drug in the neutral p^H environment of the mouth. For Polyanionic hydrogels were developed for colon specific drug delivery system. Swelling of such hydrogels in the stomach is minimal and thus drug release is also minimal. The extent of swelling increase as the hydrogel passes down, the intestinal tract due to the increase in pH leading to ionization of the carboxylic groups.[18,19]

Freeze/Thaw Method of Preparation

Hydrogel preparation involves physical cross-links due to crystallite formation. These method does not require the presence of a cross-linking agent such physically crosslinked materials also exhibit higher mechanical strength than chemical or irradiative techniques because, the mechanical load can be distributed along the crystallites of the three dimensional structure. On the other hand, physical hydrogels of PVA generated by a Freeze- thaw cycles have in their opaqueness a major drawback for ophthalmological applications. For ex aqueous PVA+PAA solution has the unusual characteristics of crystallite formation upon repeated freezing and thawing cycles. The number and stability of these crystallites are increased as the number of freezing/ thawing cycles is increased, freezing/ refrigeration 0±2ºC for 2 hours and thawing 25±2ºC for 1 hr. Advances in fundamental and applied biomedical sciences rely on enhanced understanding and a superior level of control over biomaterials, from their synthesis and manufacturing to the design of materials properties, both surface and bulk. There dimensional swollen macromolecular networks, offer unique possibilities to engineer materials with properties closely matching human tissue Specifically with regard to mechanical properties, water content and accessibility to solutes. While chemically crosslinked gels dominate the field, association of polymers through non-covalent linkages, i.e. Physical hydrogels is more friendly toward fragile biological cargo and is therefore highly attractive for biomedical applications. Among these, physical hydrogels based on poly (vinyl alcohol), PVA, stand out due to their superior mechanical properties and biocompatibility. These gels are typically obtained through cryogelation, i.e. a benign and non- harmful procedure of freezing- thawing of polymer solutions; a technique which yields robust PVA based materials with excellent mechanical properties, biocompatibility and stability. Regretfully, PVA cryogels largely failed to meet the requirements of nano-medicine (nanoscale precision in materials design, controlled drug release, and degradation) and as such have not become a common tool for biomedical engineering. Poly (vinyl alcohol) PVA is well known polymer which can generate hydrogels by physical or chemical cross-linking. PVA has been used to develop new materials for

different areas such as intelligent polymers, medicine, drug release, sensors, and cell encapsulation material. Etc. One important feature of PVA hydrogels (PVA HG) is the ability to change their mass, volume, and density in contact with electrolyte solution by a certain quantity of water which was firstly retained by the hydrogel. These modifications could be explained by water elimination from the hydrogels that initially reached the equilibrium of swelling. Polyvinyl alcohol, henceforth referred to as PVA, has become a prime candidate for improved biomaterials and drug delivery systems. PVA is a relatively inert polymer which is easily processable. PVA is hydrophilic and therefore swells in the presence of water or biological fluids to form hydrogels. This properly is particularly useful because it can allow for the release of drugs incorporated into these hydrogels. Other polymers such as polyacrylic acid (PAA) and polyethylene glycol (PEG) can be blend with PVA to impart additional properties such as pH- sensitivity or improved blood response. One problem with preparation of such biomaterials is the use of crosslinking agents and other reacting to form networks needed to product stable materials. This agent may include glutaraldehyde and formaldehyde, among others. Any residual material left after the formation of the polymer networks may reach out and cause harm to the body, as these agents are generally toxic. Thus, alternative methods of forming polymer networks or gels have been studied. In PVA films, crystallites that stabilize the material can be formed either by freezing and thawing cycles or by annealing using heating and cooling. These techniques form useful stable biomaterials without addition of toxic adjuvants. Physical mixtures and secondary bonding: In addition, hydrogels are formed by polymer blends between chitosan and other water- soluble nonionic polymers, such as poly vinyl alcohol (PVA). After a lyophilization or a series of freeze- thaw cycles. These polymer mixture forms junction points in the form of crystallites and inter-polymer complexation. The chain-chain interactions perform as cross-linking sites of the hydrogel formation. In the case of Chitosan- PVA polymer blends, increasing the chitosan content negatively affects the formation of PVA crystallites leading to the formation of poor hydrogel structures.

Cryogenic Gelation

Among the various techniques to effect PVA gelation, a cryogenic route is most well studied and widely employed. This technique was pioneered by Peppas *et. al.* and subsequently attracted significant research attraction as an approach to produce robust hydrogels for biomedical applications. Cryogels are gels matrices prepared by freezing and subsequently thawing an initially homogenous polymer solution, The initial freezing occurs at subzero temperature resulting in formation of ice crystals, the latter action as porogen material within a polymer matrix, while gradual thawing yields polymer enriched microphases and association of the polymer chains. The two factors together contribute to a high porosity of the cryogels with typical pore sizes in micrometer range and a non hindered diffusion of solutes and mass transfer. cryogel prepared as monoliths are elastic, sponge-like gels, and pore sizes of up to a hundred micrometers can be reached. It is generally accepted that degree of physical crosslinking of PVA chains increases with consecutive freeze-thaw cycle. Mechanical properties of the gels can be controlled by parameters of cryogelation i.e. thawing rates and holding times, and polymer concentration, rather than molecular weight, appeared to be a tool of control over the properties of cryogels. Addition of DMSO into aqueous polymer solution was shown to aid controlling both tensile strength of the cryogels and their porosity. According to the proposed mechanism, DMSO reduces the amount of ice formed and avoids phase separation thus reducing porosity within the cryogels. It was shown that the drug was released as a function of hydrogel swelling and it is therefore possible to tailor the drug release kinetics by controlling the physical crosslinking in the PVA matrix. The method is fast, inexpensive, and useful when dealing with poor water soluble drug.[4,9,10,11]

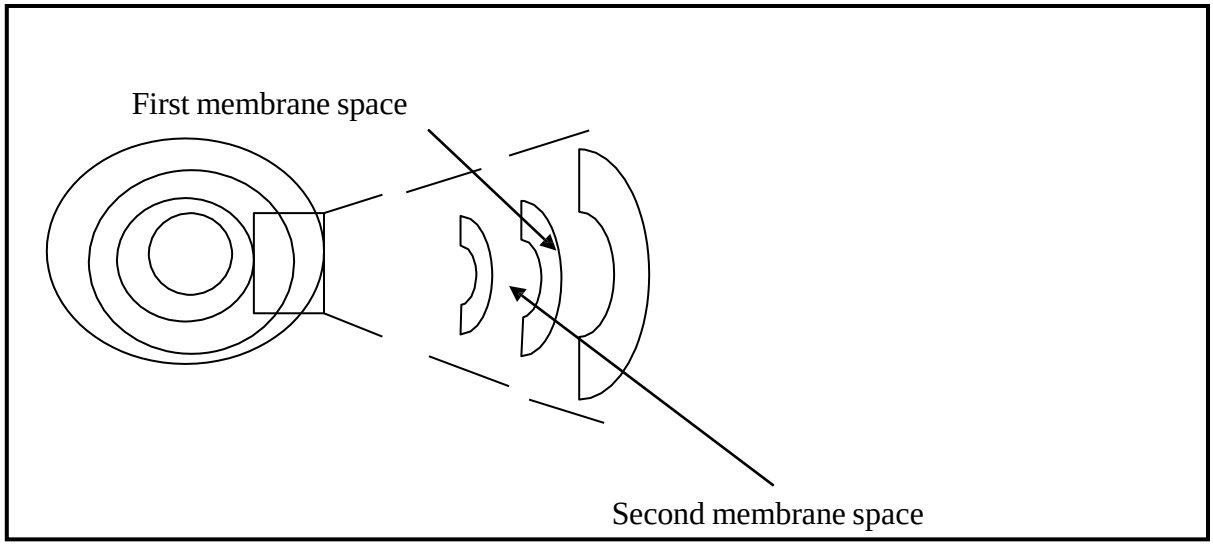

Figure 1: Multimembrane onion like physical hydrogel

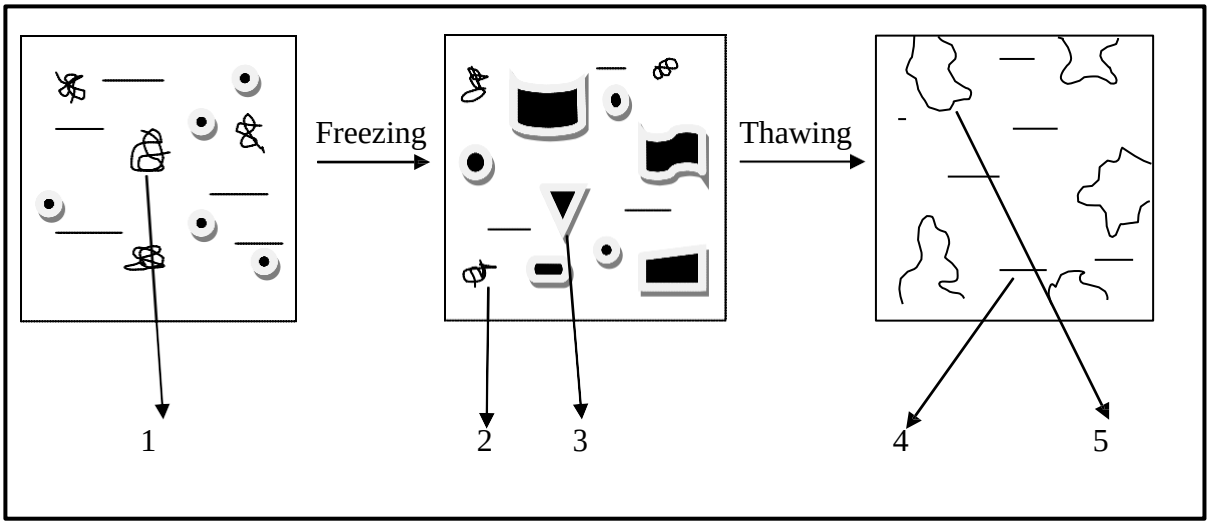

Figure 2: Illustration of a freeze- thaw treatment yielding highly porous PVA physical hydrogels, 1: Macromolecules in solution, 2: Liquid microphase, 3: Frozen solvent, 4: Macropores 5: Polymer network.

Table1: Drugs, BCS class, Polymers, Conc, Cycles and (F-T)

S. No.	Drug	BCS class	Polymers	Conc	Cycles (F-T)	Reference
1	Dexamethasone	2	PVA	5% w/w	-20ºC, 16 hrs. Room temp. 8 hrs. 1or 2 cycles.	AAPS J, 2005; 7 (1) : E231- E240.
2	Dexamethasone	2	PVA	2.5,5,7.5, 10% w/v	-20ºC, 1 hrs. Room temp. 30 min. Eight cycles.	J Mater Sci: Mater Med, 2002;13 : 29-32.
3	Ciprofloxacin HCl	4	PVA	5,7,10 and 15% m/m	-15ºC, 100ºC. One cycle.	Int J Pharm, 2007 ; 343 : 34-40.
4	Ciprofloxacin	4	PVA+	PVA/Starch weight	-20ºC, 24hrs.	Bull Mater Sci, 2011 ; 34(7) : 1739-

	HCl		Starch	fraction 20/80,33.3/66.7 and 42.8/57.2	Room Temp. 1 hrs. At least Three cycles.	1748.
5	Sulfadizine silver	2	PVA and Chitosan	PVA- 7.5% Chitosan- 0.5, 0.75 and 1.0%	-20ºC, 18hrs. Room Temp. 6 hrs. Minimum Three cycles	J Pharm Bioallied Sci, 2012 : S53-S56.
6	Theophylline	1	PVA	15 and 20% wt	-20ºC, 6 or 12 hrs. 25ºC, 2hrs. Two- three cycle.	Eur J Pharm Biopharm, 1997; 43 : 51-58.
7	Theophylline	1	PVA		-20ºC, 2 to 24 hrs. 25±1ºC, 2 to 24 hrs. Two to nine cycles.	J Memb Sci, 1995; 107 : 229-237.
8	Naproxen sodium	2	Acrylamide + MBAAm	0.765gm in 20 ml water	-18ºC, 16 hrs. room temp.	J Pharm Pharmcol, 2014 ; 2 : 527-533
9	Aspirin	1	PVA and PAA		-80ºC, Room temp. Up toTen cycles	Afr J Pharm Pharmcol, 2014 ; 8 (24) : 674-684.
10	Ketanserin	2	PVA		-20ºC, 12hrs. 25ºC, 2 hrs. Two cycles.	J Biomater Sci Polym Ed, 1996 ; 7(12) : 1055-1064.
11	Atenolol	3	PVA	10% wt	-20ºC, 16 hrs. Room temp. 8 hrs. Five cycles.	J Saudi Chem Soc, 2010 ;14 : 237-240.
12	Clindamycin	1	PVA + Sodium alginate	PVA- 10% w/v SA -3% w/v	-20ºC, 18 hrs. Room temp. 6 hrs. Three cycles	Biol Pharm Bull, 2008 ;31(12) :2277-2282.
13	Propranolol HCl	1	PVA	10,15 and 20% w/w	-20ºC, 15 hrs. 5ºC, 24 hrs.	Chem Pharm Bull, 1989 ; 37(9) : 2491-2495.
	Atenolol	3				
14	Indomethacin	2	PVA MP Sorbitol	PVA - 10,15,20,25 and 30 %w/v MP- 0,1,2,3 and 4 % w/v Sorbitol- 0,10,20,30, and 40 % w/v	-20ºC, 25ºC. Four Cycles.	Arch Pharm Res, 1993 ;16(1) :43-49.
15	Indomethacin	2	PVA PAA	PVA- 8,10,15,20,25% PAA/PVA% wt fraction- 0/100,	-10ºC, 15 hrs. 4-5ºC, 24 hrs.	Pharm Res, 1989 ; 6(4): 338-339.

				10/90,20/80, 30/70,40/60 and 100/0		
16	Econazole nitrate	2	PVA	10,15and 20% w/v	-12ºC, 16 hrs. Room temp. 8 hrs. Four, six and eight cycles.	J Drug Del, 2014 : 1-14.
17	Captopril	3	PVA	2%w/w	-30ºC, 48 hrs. 4-5ºC, 24 hrs.	Acta Pharmacol Sin, 2000,21 (7) : 591-595.
18	Ephedrine HCl	1	PVA	10,12,14, 16 and 18% w/v	-20ºC, 12 hrs. 15ºC, 12 hrs. Repeated Three cycles.	Colloid Polym Sci, 2014 ; 292 : 1665 -1673.
19	Pentamidine	4	PVA PLGA	0,3 and 6% w/v 5,10, and 15% w/v	-20ºC, 16 hrs. Room temp. 8 hrs. One full cycle.	Pharm Res, 2002 ; 19(11) : 1713-1714.
20	Rosiglitazone maleate	2	PVA+ Chitosan + Glyoxal	PVA 4% w/w Chitosan 2,4,6 ,and 8% w/w Glyoxal 2,4,6 and 8% w/w	-60ºC, 12 hrs. Room temp. 4 hrs.	Daru , 2010 ; 18 (3) : 200-210.
21	Ampicillin sodium	3	PVA+ Hydroxy ethyl starch	not given	-20ºC, 18hrs. 25ºC, 6 hrs. Three cycles.	Arabian J Chem , 2014 ; 7 : 372-380.
22	Oxprenolol	1	PVA	15 and 20% wt	-20ºC, 6 or 12 hrs. 25ºC, 2hrs. Two- five cycles.	Eur J Pharm Biopharm, 1997; 43;51-58
23	Gentamicin	3	PVA+ Dextran	PVA -2.5, 3.75, 5.0, 6.25,7.5,and 10 %w/v Dextran- 0.38,0.56, 0.75, 0.94 and 1.13 %w/v	-20ºC, 18 hrs. 25ºC, 18 hrs. Three consecutive cycles.	AAPS Pharm Sci Tech, 2010 ; 11(3) : 1092-1103.
24	Insulin	4	PVA	5 and 10% w/v	-20ºC, 20hrs. Room temp. 4 hrs. One- seven cycles.	J Mater Sci:Mater Med, 2007 ;18: 2205-2210.
25	Enrofloxacin	1	PVA and Pectin	PVA 15% w/v Pectin 2.0-4.0% w/v	-18ºC for 20 hrs 25ºC for 8 hrs 3-5 cycles	Bioresour Technol, 2013;145:280-284
26	Savlon (Chlorohexidine gluconate, Cetrimede)		PVA Chitosan	PVA/ CS fraction 2.9,3.0,4.0,5. 6,6.0,8.2 and 12.1	Three cycle	Biomatter,2011; 1(2):189-197

27	Aminophylline Theophylline, Ampicillin.	1 3	PVA, Chitosan, Sorbiton Sequinoleate (Castor oil) Sesame oil	PVA- 15% w/v Chitosan - 1% w/v	-20ºC for 20 hrs. 4ºC for 4 hrs. One cycle	Biol Pharm Bull, 1998 ;21(11): 1202-1206.
28	Theophylline	1	PVA,	PVA- 7% NaCl - 11%	-20ºC for 24hrs.	Int j Pharmcol, 2006 ; 2(3) :286-292.
29	Chondroitin Sulphate		PVA, chitosan	PVA- 9% w/v Chitosan- 1,2 and 5% w/v	-20ºC for 24 hrs. Room temperature 4 hrs. Four cycles	J Biotechnol Biomater, 2012 ; 2(4) .
30	Clindamycin	1	PVA, Sodium alginate	PVA- 10% w/v SA- 3%	-20ºC for 18 hrs. Room temperature for 6 hrs. Three cycles.	Biol Pharm Bull, 2008 ; 31(12):2277-82
31	Nill	0	PVA Amorphus Sulfonated Polyesters	PVA- 10% w/v PES- 5% w/v	-22ºC for 17 hrs Room Temperature	Mater Res, 2007 ; 10(1):43-46
32	Nill	0	PVA Sodium decylsulfate	PVA 11wt%	-22ºC for 22 hrs. 25ºC for 4hrs. One - nine cycles	J Phy Chem B, 2007; 111: 2166-2173
33	Nill	0	PVA	not given	-20ºC for 12 hrs. 25ºCFor 12 hrs. One - three Cycles	Proc Estonian Acad Sci, 2009 ,58 (1) :63-66
34	Nill	0	PVA	PVA - 10 to 16 % w/v	0ºC ± 2ºC 37ºC ± 2ºC 15-45 cycles	Biomed Mater, 2012; 7.
35	Nill	0	PVA	not given	-25ºC for 24 hrs. 25ºC for 24 hrs. One cycle .	J Polym Sci: Polym Phy , 1997 ; 35 ; 2421-2427.
36	Nill	0	PVA, Water Soluble chitosan	PVA -7 % Wt WS chitosan -2% wt Glycerol - 1% wt	-20ºC for 24 hrs. 25ºC for 24 hrs. One cycle	J Appl Polym Sci, 2008 ;108 :1365-1372

			Glycerol,.			
37	Niil	0	PVA, Glycidyl acrylate, Glutaradehyde HCl	20 % PVA- Acrylate	-15ºC for 24hrs. Room temperature 24 hrs. Two cycles	Polym, 2004 ; 41 :7715-7722.
38	Nill	0	PVA, Collagen	2.5,5,8,10 and 15% w/v	-30ºC for 12 hrs. Room temperature. 1-16 cycles	J Mater Sci: Mater Med,1993 ; 4 :538-542
39	Nill	0	PVA, PAA, DMSO,water.	PAA/PVA-0/100, 10/90,20/80,30/70, 40/60 and 100/0		J Mater Sci, 2006 ; 41 : 2393-2404.
40	Nill	0	PVA, KCl, NaCl	PVA- 11.14 % w/v.	-15ºC for 12 hrs. room temperature 12 hrs. Three cycles.	Eur Polym J, 2007 ; 43 : 460-467.

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