

Department of Pharmaceutical Technology¹, Slovak Medical University;
Department of Galenic Pharmacy², Faculty of Pharmacy, Comenius
University, Bratislava, Slovak Republic

Chitosan hydrogel with terbinafine – an evaluation of drug release

D. MATUŠOVÁ¹, Z. VITKOVÁ², E. TRUPLOVÁ¹, P. HERDOVÁ²

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Pharm. Desana Matušová, Ph.D., Department of Pharmaceutical Technology, Slovak Medical University, Limbová 12, 83303 Bratislava, Slovak Republic
desana.matusova@szu.sk

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The aim of this study was to evaluate rheological properties and release of terbinafine (an antifungal drug) from chitosan hydrogels, and test some additives as possible solvents, preservatives and potential chemical penetration enhancers. The release of terbinafine was better from hydrogel with glycerol (plastic flow), than that from hydrogel with propylene glycol (thixotropic flow), the presence of Tween 80 showed a negative influence on drug release from both types.

Chitin is one of the most abundant natural biopolymers. This linear polysaccharide is usually prepared from crabs, shrimp and other crustaceans; it can be obtained from insect bodies, fungi, moulds and some algae. According to microfibrils' orientation there are three polymorphic forms of chitin – α , β , γ . Most common is α -chitin (Majtán et al. 2007). The units of chitin (*N*-acetyl-D-glucosamine) can be partially deacetylated by building chitosan – a polymer, composed of randomly distributed acetylated units and deacetylated units (β -(1-4)-linked D-glucosamine), the presence of amino groups causes good solubility of chitosan in weak organic acids. In commercial chitosans the degree of deacetylation ranges from 60 to 100%, creating complexes with molecular weight from 3–6 kDa (oligomeric derivatives) up to over 10^6 Da – long chain derivatives. Chitosan is used in oral dosage forms (for sustained release, as oral mucoadhesive, as antihyperlipidemic, some types are intestinal absorption enhancers), topical drugs (powder, gels, films, used e.g. as hemostatics or wound dressings), parenteral administration (nanoparticles, excipients for gene transcription) (Kato et al. 2003, Matušová and Truplová 2007). It has antimicrobial activity and it does not induce hemolysis (Jumaa et al. 2002). Terbinafine is an antifungal drug with excellent *in vitro* activity against filamentous fungi, moulds and yeasts like *Trichophyton* spp., *Aspergillus* spp., *Microsporum* spp., *Candida albicans* and others (Jessup et al. 2000). It is used in oral dosage forms and also for topical administration. On the Slovakian pharmaceutical market only one suspension gel containing terbinafine – Lamisil® gel – is available. The concentration of terbinafine in Lamisil® gel is 1% and the gel creating agent is Carbomer 934P. The study was focused on a new gel creating agent from the group of biodegradable polymers – chitosan. In this work we formulated chitosan gels containing terbinafine (1% or 2%),

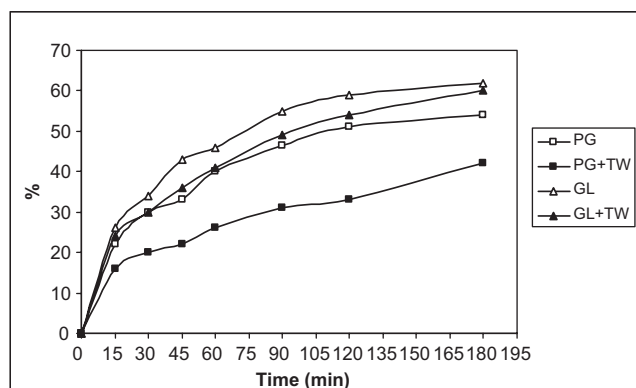


Fig. 1: Time dependence of terbinafine release from hydrogel in relation to additives. Hydrogels (2.5% chitosan contained 1% terbinafine and different additives: (PG – propylene glycol, PG + TW – propylene glycol and Tween 80, GL – glycerol, GL + TW – glycerol and Tween 80)

we measured structural viscosity and drug release (release of terbinafine) from these gels.

By assessing the terbinafine release from 2.5% chitosan hydrogel it was found that the 1% concentration of the drug is preferable, the amount released from hydrogel with 1% of terbinafine was greater than that from hydrogel containing 2%, a similar result was found by Vitková et al. (2008). Therefore, we continued the work with hydrogels containing 1% of terbinafine only. Ethanol, propylene glycol, glycerol and Tween 80 were used in the role of solvents, preservatives and chemical penetration enhancers.

The terbinafine release from chitosan hydrogels was better in the presence of humectants (glycerol or propylene glycol) used in concentration of 10% according to the gel without them. Glycerol increased the drug release more than propylene glycol as follows from Fig. 1.

The influence of Tween 80 on drug release was studied as well. The study reveals that a concentration of 0.1% decreases drug release from the hydrogel. This may be caused by the fact that this concentration is above CMC value; the drug molecules may be trapped inside the micelles.

The evaluation of rheological properties showed that chitosan hydrogel with terbinafine and propylene glycol (PG) exhibit thixotropic properties, see Fig. 2, while the hydrogel with glycerol (GL) is plastic. This could be also the reason of different drug release from these hydrogels.

Based on the results obtained it could be concluded that humectants play a significant role in terbinafine release. For the formulation of terbinafine into chitosan hydrogels glycerol is more acceptable humectant than propylene glycol.

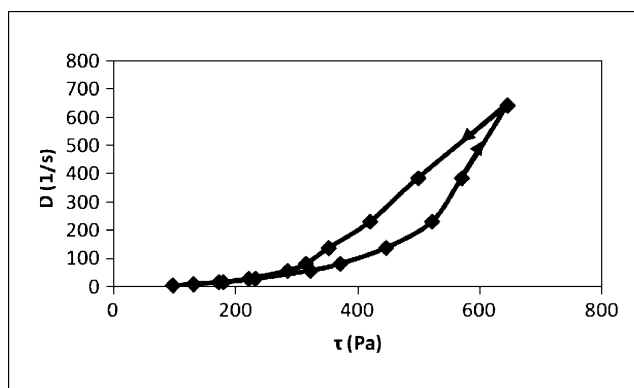


Fig. 2: Rheogram of the chitosan hydrogel with terbinafine and propylene glycol (PG)

Experimental

1. Materials

Terbinafine hydrochloride (TB) – [*N*-(2E)-(6,6-dimethyl-2hept-2-en-4-ynyl)-*N*-methyl-(1-naphthylmethyl)] amine hydrochloride – obtained from Zentiva a.s. Hlohovec (SR) was used without purifying. Chitosan, ethanol 96%, propylene glycol, glycerol, lactic acid, Tween 80, NaCl, cellophane.

2. Instruments

Spectrophotometer – Philips Pyll Unicam Ltd., Cambridge (United Kingdom); Permeation apparatus - R&D laboratory of the Department of Galenic Pharmacy, Faculty of Pharmacy, Comenius University in Bratislava.

3. Preparation of the hydrogel

2.5% chitosan hydrogels containing lactic acid solution were prepared without and with 1% or 2% terbinafine. Other additives were: Ethanol 96%, Propylene glycol (10%), Glycerol (10%), Tween 80 (0.1%). The mixture was homogenised and left to stand for 48 h.

4. Evaluation of terbinafine release

A series of six permeation chambers was used. An amount of 3.0 g of the studied hydrogel was placed in the donor chamber and 20 ml of isotonic NaCl solution was placed into each acceptor part. The acceptor phase was mixed with a magnetic stirrer. Terbinafine was left to permeate at 37 °C through a hydrophylic membrane into the isotonic NaCl solution. The amounts of the released drug were determined by spectrophotometry at $\lambda = 284$ nm after 15,

30, 45, 60, 90, 120 and 180 min. The results were evaluated from released cumulative amounts of the drug and represent averages of 6 measurements.

5. Determination of rheological properties

Rheological properties were measured by Viscotester VT 500 (Haake Mess-Technic GmbH, Germany) at 20 °C, 48 h after hydrogel preparation (three parallel measurements).

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