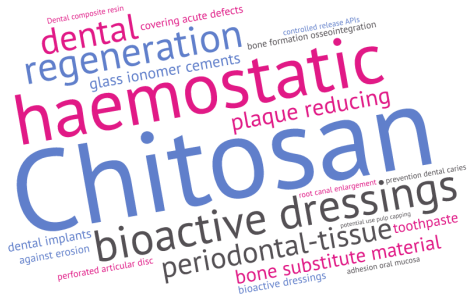
Chitosan a biopolymer for dental applications

Expertenpanel „Biomaterialien“ am 08.12.2016 in Mainz



Katja Richter, Geschäftsführerin
Heppe Medical Chitosan GmbH, Halle (Saale)

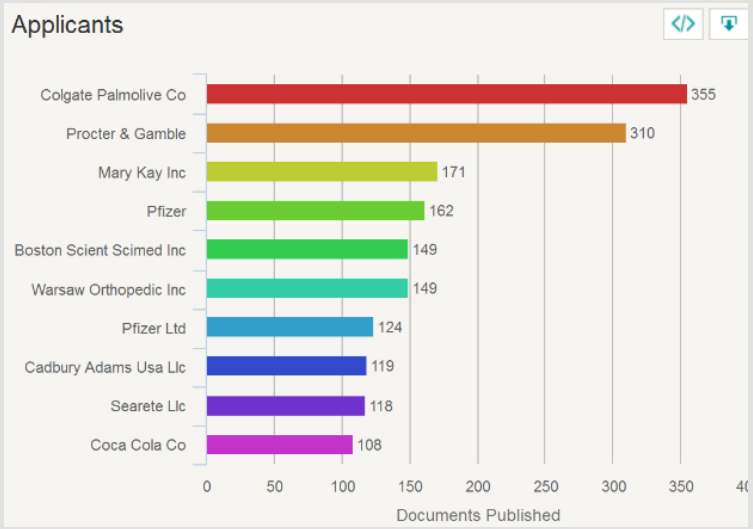
Did you know?

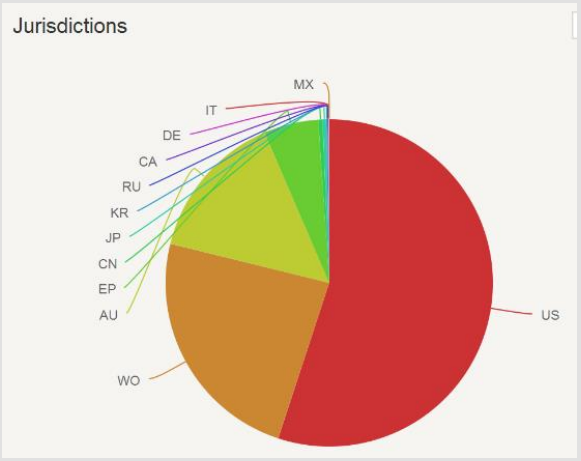
Searching for chitosan and dental applications…

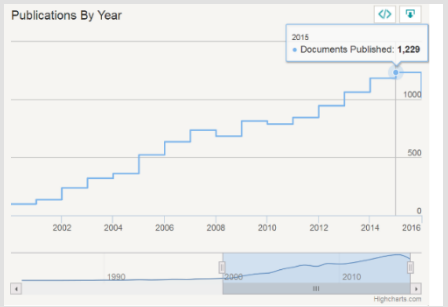
Over 1,900,000 results on google

Over 12,000 results on found on google patents

287 articles found on pubmed







Source:
www.lens.org
https://www.ncbi.nlm.nih.gov/pubmed/
https://patents.google.com

Agenda

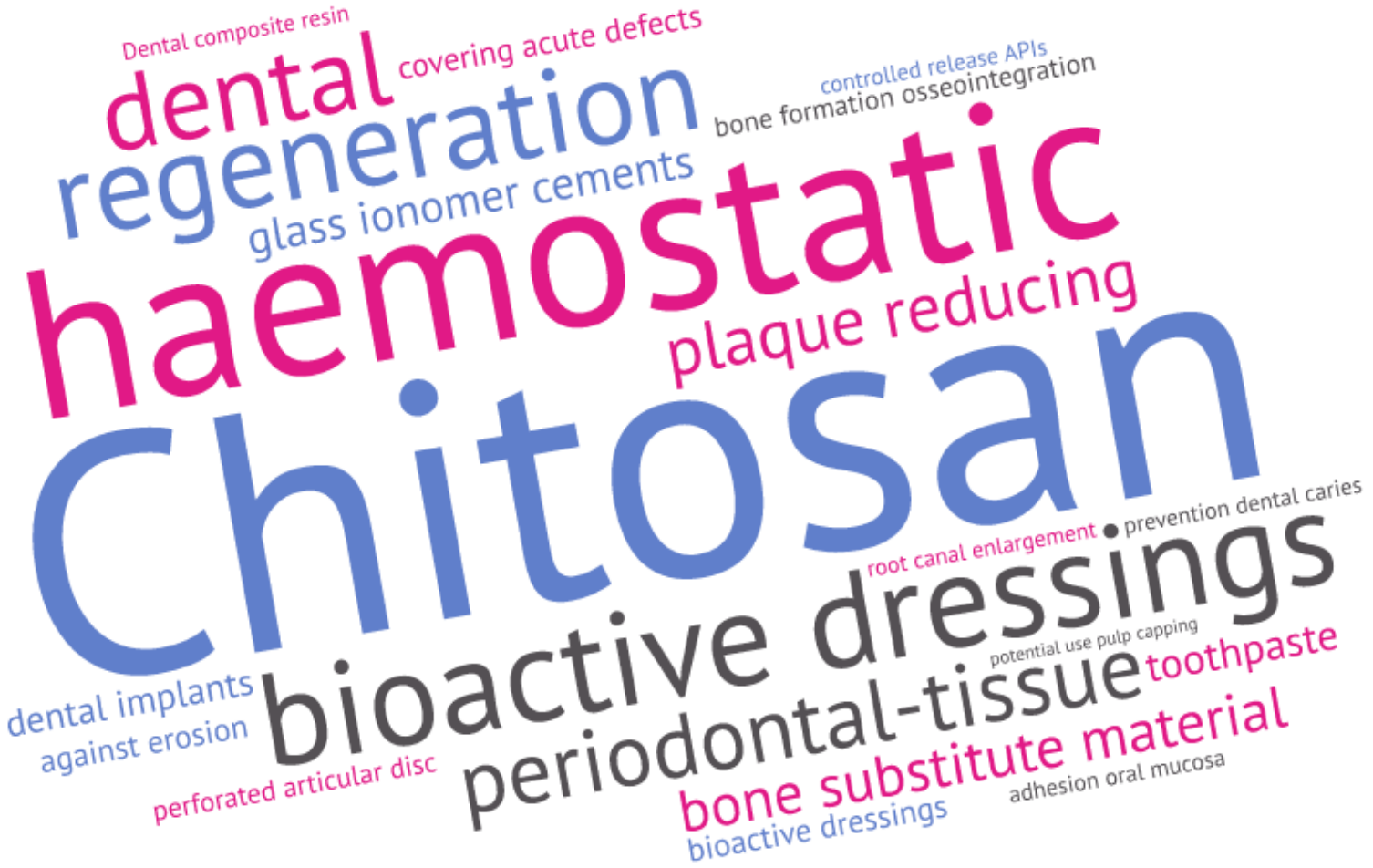
Chemical aspects

- **Chitin**
- **Chitosan**

Biological functions

- Properties
- Applications

Dental Application

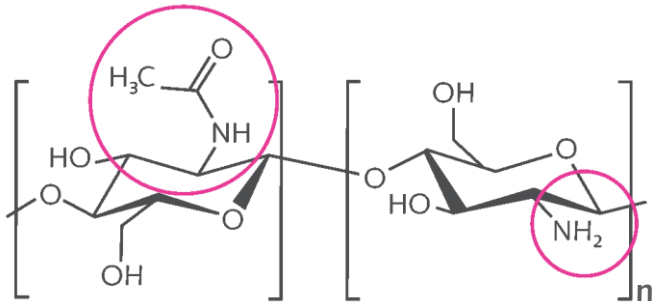


Chitin – chemical aspects

Crustacean → Basic raw material ← Fungi, insects,…

Decalcification (HCl)

Deproteinisation (NaOH)



Chitin

Deacetylation (DA)

Chitosan

MW

Derivatisation

DA

To upgrade product properties

Drug-formulation

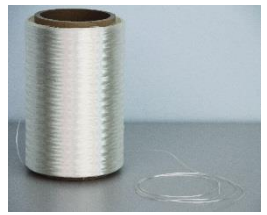
(e.g. ophtalmology, drug delivery)

MedTech

(e.g. wound dressing, coating)

Texturing

(High-Tech materials)



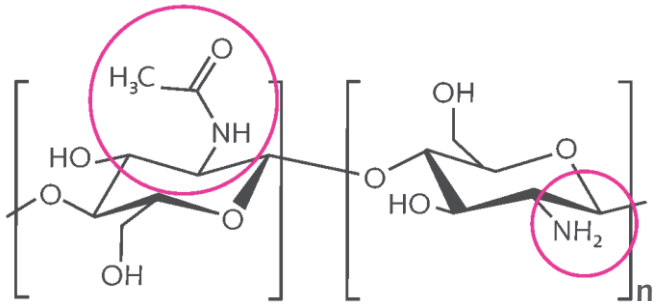
- **Chitin** is second most common regenerative polysaccharide after cellulose
- nitrogenous polysaccharide
- monomers of chitin are called acetyl-glucosamine because the acetyl group is bonded to the nitrogen a
- three different kinds of structure in which chitin occurs in nature:
  - α chitin
    (in arthropods, crustaceans)
  - β chitin
    (in molluscs, such as squids)
  - γ chitin
    (a mixture of alpha and betastructures, notably in cephalopods)

Chitosan – chemical aspects

Crustacean → Basic raw material ← Fungi, insects,…

Decalcification (HCl)

Deproteinisation (NaOH)



Chitin

Deacetylation (DA)

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- **Chitosan** is a derivative of chitin
- natural linear amino-polysaccharide
- monomer of chitosan is glucosamine
- cationic polymer
- structure is based on repetitive D-glucosamine units (deacetylated units), and fewer randomly distributed N-acetyl-D-glucosamine units (acetylated units), linked by β-(1-4) bond
- is made by N-deacetylation of chitin

Chitosan derivatives

Commercially, chitosanS usually have a DDA in the range of 70–95% and a molecular weight of 10^4–10^6 g/mol

- chitin and chitosan derivatives are extremely versatile
- most of them are directly soluble in water
- depending on their derivatization, can be applied in neutral and basic pH ranges

- Our standard derivatives include:
  - Chitosan HCl
  - N, O-Carboxymethyl-Chitosan (CMC)
  - Chitosan Lactate
  - Chitosan Acetate
  - Chitosan Glutamate

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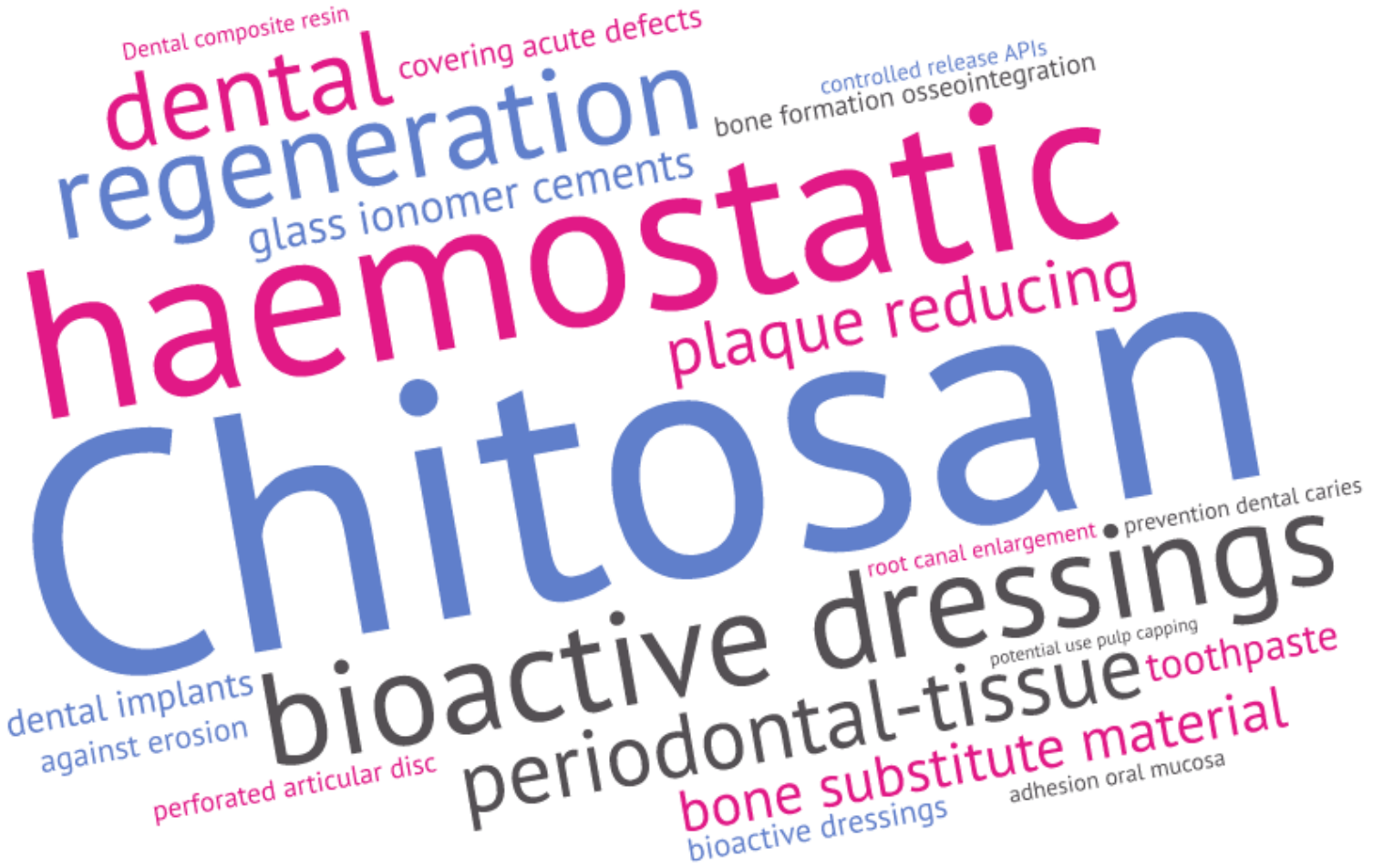
+ Chitin
+ Chitosan

Biological functions

+ **Properties**
+ **Applications**

Dental Application



Chitosan properties I

- Solubility:
  - soluble in almost all diluted acids with a pH below 6.0 (pKa=6.3)
  - insoluble in sulphuric acid and water
- biodegradable by enzymes (lysozyme, papain, pepsin)
- non-toxic, biocompatible
- detected in the human body as an endogenous substance
- having a stimulating effect on the immune system and metabolism
- anti-inflammatory
- haemostatic, wound-healing
- inhibiting the growth of bacteria and fungi
- film- and fibre-forming, cross-linking
- odour-absorbing, capable of bonding to proteins, heavy metals, suspended solids

Aranaz et al, Functional Characterization of Chitin and Chitosan, Current Chemical Biology, 2009, *Vol. 3, No. 2*

Table 3. Relationship Between Chitin and Chitosan Biological Properties and their Characteristics

Property	Characteristic
Biodegradability	DD, distribution of acetyl groups, Mw
Biocompatibility	DD
Mucoadhesion	DD, Mw (only chitosan)
Hemostatic	DD, Mw
Analgesic	DD
Adsorption enhancer	DD (only Chitosan)
Antimicrobian	Mw
Anticholesterolemic	DD, Mw, viscosity
Antioxidant	DD, Mw

DD: deacetylation degree.
Mw: molecular weight.

Chitosan properties II

Bacteriostatic and fungistatic

- Electrostatic interaction between positively charged chitosan molecules and negatively charged bacteria membrane
- Hydrolyses of cell wall through changed permeability of cell membrane
  → loss on intracellular components

Depending on:

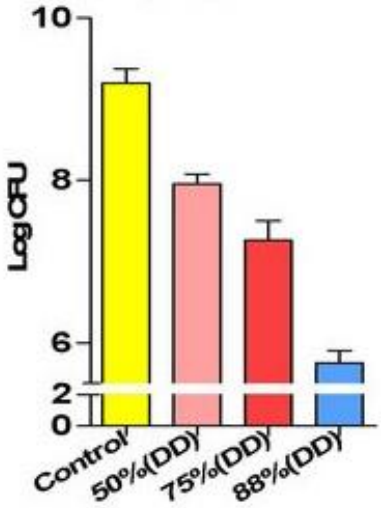
- Molecular weight (Mw) and degree of deacetylation (DDA)
  → lower Mw and high DDA, the higher the antibacterial activity
- MIC (minimal inhibitory concentration)
  → usually 0,05% to 0,1% (500 – 1000 ppm)
- pH
  → The lower the pH, the higher the antibacterial activity (< 5,9)

Aranaz et al, Current Chemical Biology, 2009, *Vol. 3, No. 2*

Table 4. Influence of Chitosan DD and Mw on Antimicrobial Activity

Physico-Chemical Property	Effect on Antimicrobial Activity
↑ DD	↑ electrostatic binding to membrane
	↑ permeabilizing effect
↑ Mw	↓ permeation into the cell nucleus

DD: deacetylation degree.
Mw: molecular weight.



Chitosan Coupling Makes Microbial Biofilms Susceptible to Antibiotics doi:10.1038/srep03364

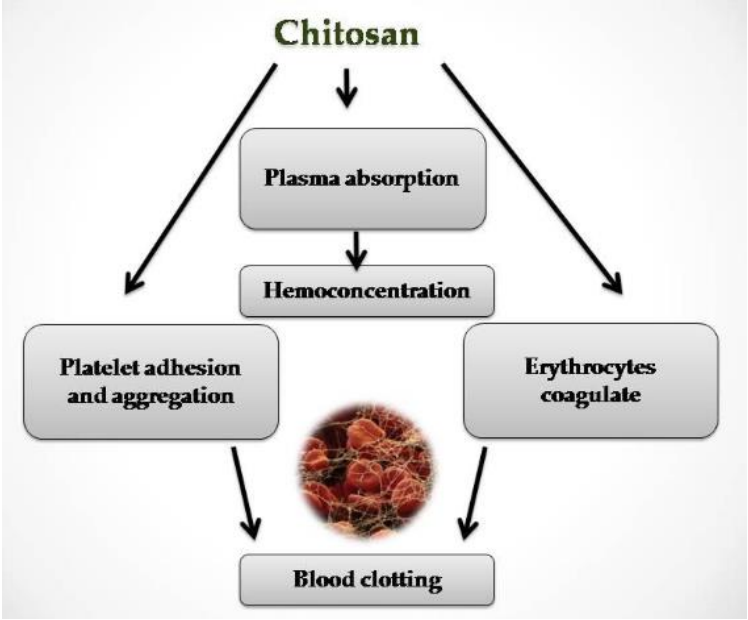
Chitosan properties III

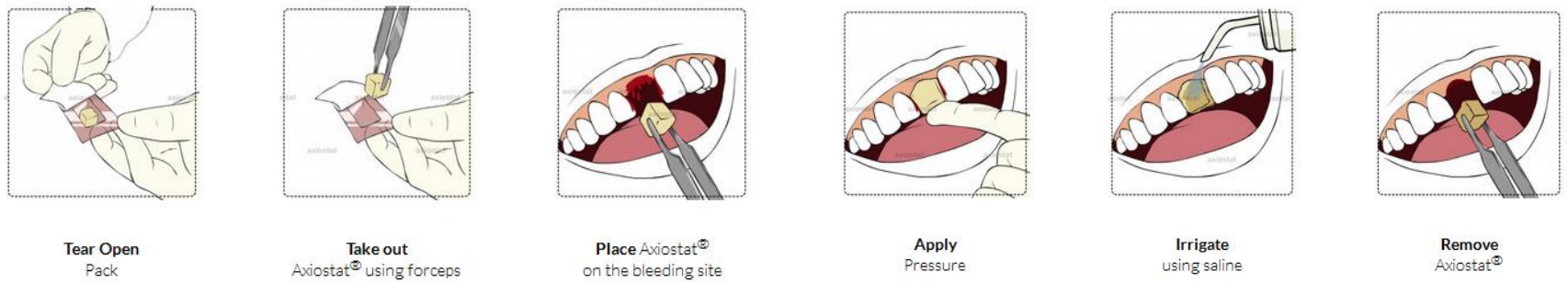
Haemostatic effect

Independent of coagulation cascade

Depending on:

- Molecular weight (Mw) and degree of deacetylation (DDA)
  → high Mw and high DDA required
- Sponges made from chitosan have the highest loading capacity of blood and water





European Journal of Medicine. Series B, 2015, Vol.(2), Is.1

www.axiobio.com

General recommodation depending on effect

Application	General Recommendations
Wound healing	High DD chitosan preferred over chitin Low Mw samples (oligomers)
Drug delivery systems	High DD High Mw
Gene Delivery	DD ≤ 80 Low Mw (around 10 kDa)
Scaffolds (tissue engineering)	DD around 85 (good proliferation and structure) High Mw (prolonged biodegradation)
Cell immobilization	Chitosan preferred over chitin (high DD)

Aranaz et al, Current Chemical Biology, 2009, *Vol. 3, No. 2*

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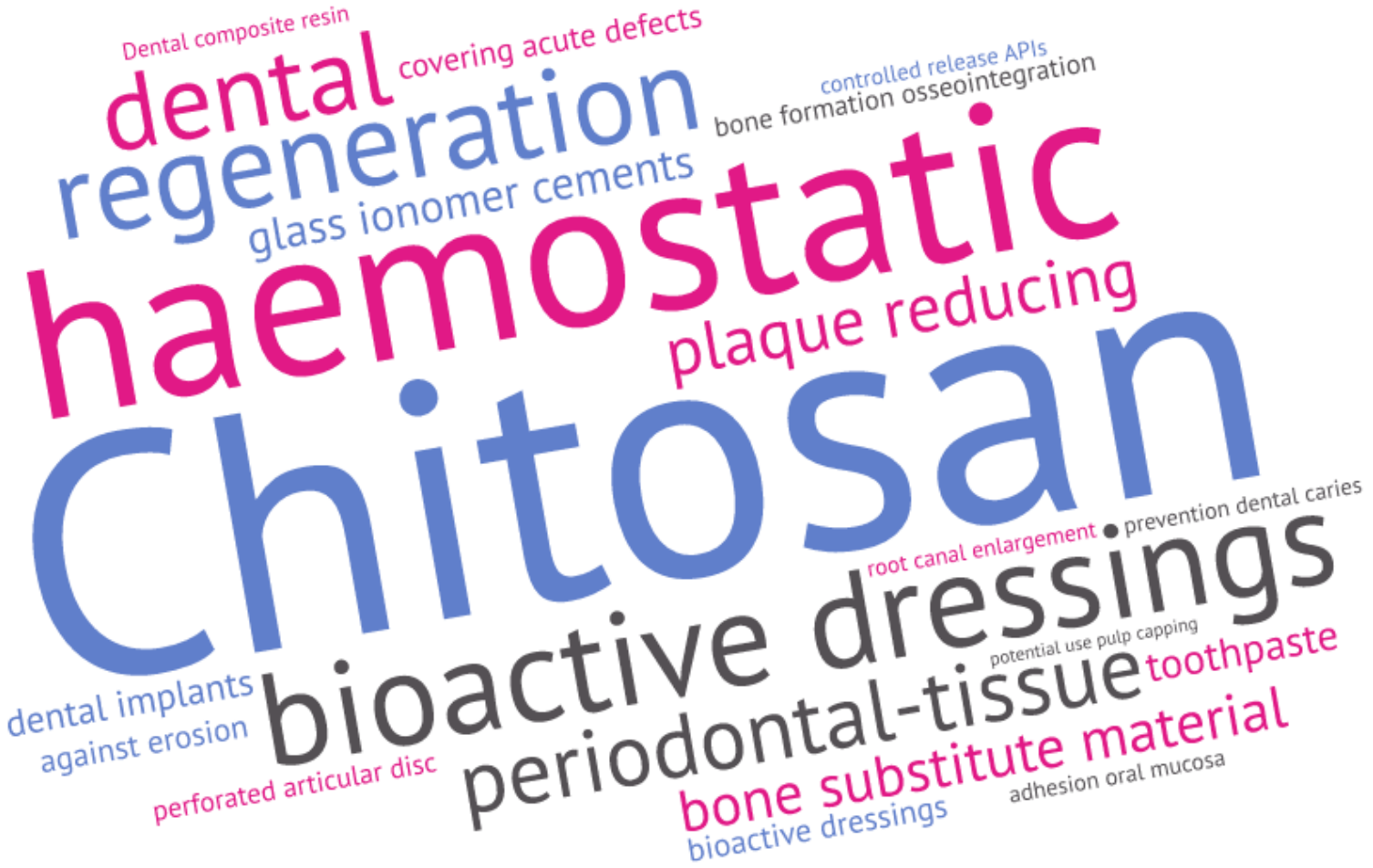
Dental Application



Dental application I

- inhibitory effect of the CS powder on *S. mutans*, and reported no statistically significant differences in mechanical properties between the chitosan-containing composite resins and the control composite resin without chitosan. Kim, J.S.; et al, *Restor Dent Endod*, 2013, 38(1), 36-42

- into root canal sealers in an attempt to disinfect root canals. They had no effect on the flow characteristic of the sealers, but they enhanced the antibacterial action, observed by a significant reduction in *Enterococcus faecalis* adherent to treated dentin. Kishen A et al, *J Endod*. 2008;34(12):1515–1520.

Table 1. The mean gray level of each zone of the sockets in case and control subjects.

Group	Coronal mean ± SD *(min ~ Max)*	Middle mean ± SD *(min ~ Max)*	Apical mean ± SD *(min ~ Max)*
Chitosan (n = 12)	35.3 ± 12.0 (21.7 ~ 60)	57.7 ± 12.3 (42 ~ 78.2)	90.9 ± 12.5 (68 ~ 110)
Control (n = 12)	34.2 ± 1.6 (22.8 ~ 57.1)	47.3 ± 13.4 (31.7 ~ 76.3)	64 ± 16.5 (34.3 ~ 95.5)
P value*	0.583	0.05	0.002

*Wilcoxon Signed Rank Test.

Table 2. Ratio of regenerated bone density to the maximum mandibular bone density at the three zones in chitosan-filled and control groups.

Group	Coronal *% ± SD*	Middle *% ± SD*	Apical *% ± SD*
Chitosan (n = 12)	37.8 ± 9.8	61.9 ± 7.9	98.2 ± 3.9
Control (n = 12)	37.3 ± 11.6	51.1 ± 13.1	68.9 ± 14.6
P value *	0.896	0.040	0.000

* Paired t-test.

F. Ezoddini-Ardakan et al., / Health 3 (2011) 200-205

Dental application II

Mini-Reviews in Medicinal Chemistry, 2016, *16,*
Clinical Application of Chitosan in Dental Specialities, Mieszko Wieckiewicz et al,

Dental specialties	Chitosan applications	Type of research	Year of publication	Authors
Conservative dentistry	-Direct pulp capping	*In vitro*/ *In vivo*	2006/2014	Matsunaga *et al.* and Li *et al.* [24, 25]
	-Antibacterial against *S. mutans*	*In vitro*	2013	Kim and Shin [22]
	-Component of toothpaste against erosion/abrasion included demineralised dentine matrix	*In vitro*	2014	Ganss *et al.* [23]
	-Indirect pulp capping	*In vitro*	2015	Chen *et al.* [26]
Endodontics	-Antibacterial against *E. faecalis* using new photosensitizer	*In vitro*	2010/2012/2014/ 2014/2015	Shrestha *et al.* [28-32]
	-Sustained release of calcium ions from the calcium hydroxide in the root canal system	*In vitro*	2010/2014	Ballal *et al.* and Grover and Shetty [33, 34]
	-Improving stability of dentin collagen	*In vitro*	2011	Shrestha *et al.* [38]
	-Removal of smear layer after root canal instrumentation	*In vitro*	2013	Silva *et al.* [37]
	-Inhibition of biofilm by incorporation with zinc-oxide eugenol-based sealer	*In vitro*	2013	DaSilva *et al.* [39]
	-Regulation of stem cell differentiation from apical papilla	*In vitro*	2014	Shrestha *et al.* [35]
	-Ingredient of triple antibiotic intracanal paste against *Candida albicans* and *E. faecalis*	*In vitro*	2014	Shaik *et al.* [36]

Dental application III

Dental specialties	Chitosan applications	Type of research	Year of publication	Authors
Oral surgery	-Guided bone regeneration	*In vivo/ In vitro/ In vivo*	2005/2007/2014	Shin *et al.*, Arpornmaeklong *et al.* and Li *et al.* [43, 45, 52]
	-Facilitate early bony consolidation in distraction osteogenesis	*In vivo*	2005	Cho *et al.* [44]
	-Bone regeneration at dental implant defects	*In vivo*	2007/2013	Zhang *et al.* and Bhattarai *et al.* [50, 51]
	-Titanium coating	*In vivo*	2007	Bumgardner *et al.* [49]
	-Hemostasis of oral surgery wounds	*In vivo*	2008/2011/2012	Malmquist *et al.*, Azargoon *et al.* and Kale *et al.* [40, 42, 41]
	-Bone tissue engineering in oral reconstruction	*In vivo*	2011	Miranda *et al.* [46]
	-New bone substitute material	*In vitro/ In vivo*	2012/2014	Bojar *et al.* [47, 48]
	-Repairing TMJ disc-Guided periodontal tissue regeneration	*In vivo*	2014	Wu *et al.* [53]
Periodontology	-Guided periodontal tissue regeneration	*In vitro*	2000/2012	Lee *et al.*and Mota *et al.* [54, 55, 56]
	-Antioxidant delivery system	*In vivo*	2000	Ozmeric *et al.* [57]
	-Epithelial attachment regrowth	*In vitro/ In vivo*	2004/2005	Fakhry *et al.* and Pang *et al.* [58, 59]
	-Antibacterial and plaque-reducing action	*In vivo*	2006	Bae *et al.* [64]
	-Treatment of periodontitis	*In vivo*	2007	Akncbay *et al.* [65]

Mieszko Wieckiewicz et al

Dental application IV

Dental specialties	Chitosan applications	Type of research	Year of publication	Authors
Periodontology	-Advanced scaffolds in periodontal tissue engineering	*In vitro/ In vivo*	2010/2012	Akman *et al.*, Liao *et al.* and Ge *et al.* [60, 61, 62, 63]
	-Antimicrobial photodynamic therapy against *P. gingivalis*	*In vitro*	2013	Nagahara *et al.* [66]
	-Periodontal ligament cells delivery system	*In vitro*	2014	Yan *et al.* [67]
Prosthetic dentistry	-Modification of glass ionomer restoratives	*In vitro*	2007	Petri *et al.* [68]
	-Antibacterial activity of composite	*In vitro*	2011	Travan *et al.* [69]
	-Antibacterial activity of dental adhesive	*In vitro*	2012	Elsaka [70]
	-Modification of lithium disilicate glass ceramic cementation procedure	*In vitro*	2014	Saker *et al.* [71]
Orthodontics	-Preventing against demineralization around orthodontic brackets	*In vivo*	2011	Uysal *et al.* [72]

Mieszko Wieckiewicz et al

Well then?

Heppe Medical Chitosan your partner for chitosanS

- Quality and variety of our chitosans is unique in the world.
- Certitude for our customers, that the behavior of our chitosan in the final product remains the same.
- State-of-the-art products Made in Germany
- ISO 9001, ISO13485 certified

DDA / Viscosity	70 %	75 %	80 %	85 %	90 %	95 %
5 mPas	70/5	75/5	80/5	85/5	90/5	95/5
10 mPas	70/10	75/10	80/10	85/10	90/10	95/10
20 mPas	70/20	75/20	80/20	85/20	90/20	95/20
50 mPas	70/50	75/50	80/50	85/50	90/50	95/50
100 mPas	70/100	75/100	80/100	85/100	90/100	95/100
200 mPas	70/200	75/200	80/200	85/200	90/200	95/200
500 mPas	70/500	75/500	80/500	85/500	90/500	95/500
1000 mPas	70/1000	75/1000	80/1000	85/1000	90/1000	95/1000
1500 mPas	70/1500	75/1500	80/1500	85/1500	90/1500	95/1500
2000 mPas	70/2000	75/2000	80/2000	85/2000	90/2000	95/2000
2500 mPas	70/2500	75/2500	80/2500	85/2500	90/2500	95/2500
3000 mPas	70/3000	75/3000	80/3000	85/3000	90/3000	95/3000

HMC+ …more than only chitosanS

HMC+ chitosan competence

- Material Know How of chitins and chitosans
- Range of deacylated chitosans
- Range of derivatives
  - Chitosan HCl
  - N, O-Carboxymethyl-Chitosan (CMC)
  - Chitosan Lactate
  - Chitosan Acetate
  - Chitosan Glutamate

→ **High grade, narrow specs**

→ **GMP compliant available**

Looking for new USPs

Jointly added value

Customer competence and needs

- Formulation know how e.g. finished product requirements
- Product and marketing competence
- Functional needs e.g. indication specific

HMC+ …more than only chitosanS

- Production of chitosan specialties as a custom manufacturer including up-scaling of custom developed processes from laboratory to production scales and contract synthesis
- Research and development with chitosan on customer request in the field of medical technology and pharmaceutics
- Anything related to chitosan: brainstorming, workshops, trainings

…additional questions?

Contact us!

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