

Food supplements for type 2 diabetics

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Abstract

Introduction. With more than 382 million patients being diagnosed with type 2 diabetes and even more unknowingly suffering of diabetes and pre-diabetes, health burden will continue to grow. Diabetes is a chronic disease, characterized by an unbalanced glucose metabolism. Insulin resistance, inhibited insulin production and rising glucose levels are on the onset of diabetes type 2. The major complications occurring in diabetics are cardiovascular disease, diabetic nephropathy, diabetic retinopathy and cognitive decline resulting in depressions and loss of memory. The pathophysiology of the complications show similarities. High glucose concentrations lead to oxidative stress and endothelial dysfunction, which is amplified by the formation of *advanced glycation products*. Endothelial dysfunction increases a bunch of intracellular cascades resulting in the onset of inflammation, vasoconstriction, cell expansion and thrombosis. This bachelor thesis hands a solution to prevent or delay the onset of these major diabetes complications by the design of a range of food supplements, especially for diabetics. Every major complication is linked to an own food supplement.

Methods. The active ingredients were chosen based on the pathophysiology of both diabetes type 2 and the complication (part 1). When the active ingredients were chosen, the excipients were discussed; a body, lubricants, moisture scavengers, firmness agents and binding agent are used to make the supplement manufacturable. To test if the excipients were added in the right amount and proportions, several tests were done. These tests include a friability test, a disintegration test and a hardness test (part 2).

Results. The active ingredients include polyphenols, vitamins, plant extracts, herbs and minerals. All supplements resulted in the acceptable ranges set for every test, contain at least one health claim and are supported by scientific evidence.

Discussion. When selecting the ingredients, several requirements were taken into account; every product should contain at least one related health claim and should be supported by scientific evidence, also affordability is taken into account. Based on these requirements,

some ingredients have been rejected. Points of discussion of these nutritional supplements are the bioavailability and interactions of some of the ingredients, such as polyphenols. Thereby, size of the tablet and quality of the used herbal extracts are points of improvements.

Conclusion. The food supplement range has reached the three most important requirements: scientific evidence, health claim and manufacturability. The range is ready for production.

Keywords

diabetes type 2, food supplements, diabetic complications, oxidative stress, advanced glycation products, microvascular disease, excipients.

Introduction

With over 382 million people around the world being diagnosed with T2 diabetes and 9% of the world population having to deal with glucose intolerance, diabetes type 2 is an immense worldwide problem (1). The estimations about the number of T2 diabetics in the near future are terrifying; diabetes type 2 rates will continue to grow in the upcoming years with 54% unto 2030. The Netherlands is not an exception in this worldwide epidemic; over 800.000 people have been diagnosed and still 200.000 people are silent-diabetics (2). In short, T2 diabetes is a complex disease which starts when the insulin-receptors become resistant to insulin. Glucose cannot enter the cells anymore and the glucose and insulin concentrations in the blood stay high. In most cases diabetes type 2 is caused by overweight and obesity. Not only is type 2 diabetes a chronic disease with an intensive treatment, also the complications of T2 diabetes can become severe (3, 4). Due to the high amounts of glucose in the blood, tissues become damaged and a low-grade-inflammation state will occur. This has striking effects on human health. The most common diabetes type 2 complications are kidney- and eye damage, cardio-vascular disease, decreased cognitive functions, depressions and low immunity (5, 6). Food can play a major role in the prevention and treatment of several diseases including diabetes type 2. The Dutch Diabetes Foundation has set nutritional guidelines, specially designed for type 2 diabetics (7). However, for a lot of type 2 diabetics it seems to be impossible to reach the recommended doses, especially regarding fruit and vegetables. Therefore, food supplements can be of major help to be less hindered by type 2 diabetes.

In this paper the major complications of T2 diabetes are discussed. Also a solution is handed by the use of food supplements. These food supplements have certain general requirements, which have to be met:

1. the supplement should have a beneficial health effect regarding type 2 diabetes complications
2. the supplement should obtain at least one relevant health claim
3. the supplement should be manufacturable

In part one the active ingredients of the supplements are chosen based on the pathophysiology of the complication, also considering health claim laws. In part two, the active ingredients are tableted into food supplements. The excipients are discussed, even as the testing of the supplements at the R&D lab. Based on these results hopefully the following question can be answered: 'How do you develop a food supplement range for type 2 (pre)diabetics from a biomedical and technological point of view?'

Part I: Design

In the case of diabetes type 2 the glucose-uptake system of the human body is disturbed. This is mainly due to the high amounts of sugar constantly available when overeating. The IR or the intracellular cascades are impaired by the higher concentrations of insulin and glucose. Glucose uptake will decrease, and in the liver glucose release will be triggered. In time, the insulin release will decrease due to exhaustion of the pancreas but the high glucose levels will stay and harm the other tissues of the human body (3). The glucose will damage the bloodvessels and they can easily form *Advanced Glycation End products (AGE's)*; proteins which are extended with a glucose-group (8, 9). The complications are mainly caused by the high glucose concentrations and AGE's leading to oxidative stress and endothelial dysfunction. Endothelial dysfunction increases a bunch of intracellular cascades resulting in the onset of inflammation, vasoconstriction, cell expansion and thrombosis. These microvascular diseases in the kidneys, eyes and brains can cause severe complications.

Methods

To assemble information about the pathophysiology of T2 diabetes and possible beneficial ingredients the literature database of Google Scholar and Maastricht University Library was used including PubMed, BioMed Central and Embase. Also, trends on the internet were followed to gain inspiration for ingredients with possible solutions for the type 2 diabetic complications. In addition, the online databases of EFSA were used to consider the ingredients to be applicable for a health claim (10, 11). Moreover, the Recommended Daily Allowances as stated in the European Union guidelines 2008/100/EG were taken into account (12). Due to confidential information, the exact amounts and recipes cannot be shown.

Results:

Diabetes type 2 has some major complications. Since these complications show slight to major differences in pathophysiology and medication, every complication was offered a separate food supplement. The most common complications of type 2 diabetes are cardiovascular disease, cognitive decline resulting in depression and memory loss, diabetic nephropathy and diabetic retinopathy. Table 1 shows the ingredients chosen for every complications. These are mainly herbal extracts, vitamins and polyphenols with antioxidant capacities. The functional properties of these ingredients are described in the official bachelor thesis.

Table 1. The functional ingredients of the different food supplements. They contain mainly polyphenols, herbal extracts, vitamins and minerals.

| | |
|------------------------------|---|
| Cardiovascular tablet | Monacolin K, Resveratrol, Fruitflow |
| Mood tablet | St. Johnswort, Vitamin B12, Calcium, vitamin D3 |
| Memory tablet | Gingko Biloba |
| Kidney tablet | Bearberry, juniperberry, vitamin B1, vitamin B6 |
| Eye tablet | Lutein, zeaxanthin, Pine Bark extract (OPC's), Vitamin B1, Vitamin B2, vitamin B6 |

Part II: Manufacturability

Background: The excipients are required to make the tablet get its shape, firmness, easiness to swallow and suitability for mass production. The active ingredients account for a maximum of 35 percent of the tablet, the rest is filled by excipients, see table 2. Due to confidential information no exact recipe of the food supplements, including the excipients, can be revealed.

Table 2: the excipients used to make a food supplement.

| | |
|---------------------------|---------------|
| Active ingredients | 30-35% |
| Excipients | 65-70% |
| Bulk | Max 60% |
| Lubricants | Max 0,8% |
| Moisture absorber | Max 0,3% |
| Firmness | Max 3% |
| Binding agent | Max 10% |

Methods: To test the supplements on manufacturability the tablets were tested using a TOMPRESS 16-D (Tom Technologies, 1999). The settings of the machine were adjusted until the right weight and thickness were reached. When, even at the highest possible pressures, the required specifications were not met, the mixture has to be adapted or a capsule could be chosen. The required specifications are characterized by the right thickness, weight, friability, disintegration and hardness. Three tests are needed to conform the specifications. The friability test is a test in which 10 tablets were placed in the ERWEKA TAR20. The percentage of weight loss after three minutes of rotation was calculated and should always be below 0.30% for a proper core of a tablet. When no coating is applied, the weight loss maximum is 1,0%. The automatic disintegration test was done using a SOTAX DT3. Six tablets were placed in tubes, and placed in a water solution at 37 degrees. When the tablet is dissolved the disintegration time is registered. The mean disintegration time was calculated. The maximal disintegration time is 60 minutes with the exception of Time-Release (TR) tablets. The disintegration time test is needed to be sure the tablet falls apart in the stomach and can be absorbed by the body. The hardness tester PHARMA-TEST PTB311E measured the thickness and the force needed to split the tablet in two. The test was done using 10 tablets. The recommended hardness range is usually given. The hardness is important since in the process of production and transportation the tablets have to withstand high forces. Therefore, the recommended hardness was set at 80 Newton. (A. Kozac, personal communication, 15 May 2014)

Results: The results of the tests described above are stated in figure 1, 2 and 3. The eye-health tablet is not integrated in the results due to missing ingredients.

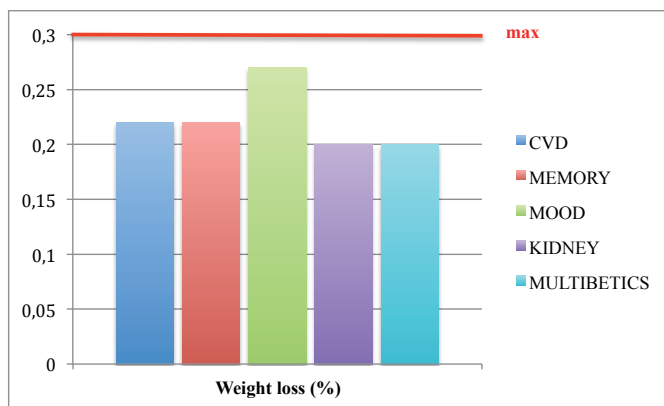


Figure 1. The results of the friability test. The red line describes the maximum limit set at 0.30 %.

Figure 1 shows the mean friability of the food supplements (n=10) measured as the percentage of the weight loss during the testing. The red line describes the limit of 0,30% weight loss in proper tablet cores. All supplements resulted in weight loss percentages underneath the limit.

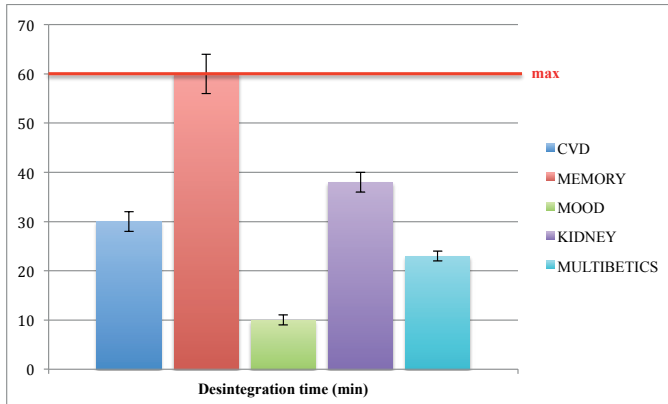


Figure 2. The results of the disintegration test. The red line describes the maximum limit set at 60 minutes.

The mean disintegration time of the food supplements (n=6) is shown in figure 2. The red line describes the limit of the disintegration time of swallowing tablets in water of 37 degrees Celcius. Gastroresistant tablets or Time-Release (TR) tablets need to be disintegrated in-between 90 to 240 minutes. All food supplements, with the exception of the memory tablet, resulted below the disintegration line.

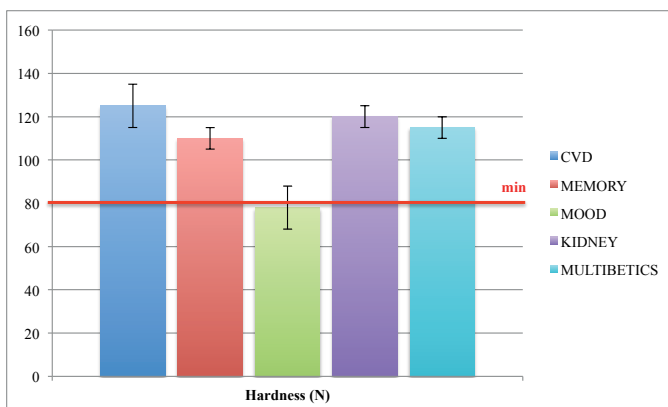


Figure 3. The results of the hardness test. The red line describes the lower aim set at 80 N.

Lastly, in figure 3 the hardness test results (n=10) are shown. The red line describes the recommended hardness needed to prevent friability and crushing of the tablets during processing and transportation. Lozenge tablets are extremely hard and were aimed at 300 N, whereas chewing tablets were aimed at 60-90 Newton. All the food supplements, with the exception of the mood tablet, showed results above the red line of 80 Newton.

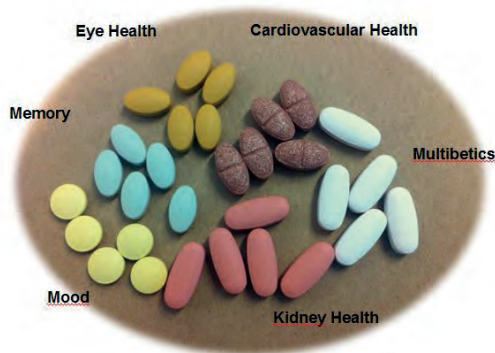
Discussion

In this section, the discussion opens about the potential of the food supplements designed to reach all the requirements. **Health effects:** Every supplement is chosen based on extensive scientific research. Some ingredients, which were not sufficiently supported by scientific research, have been left out, such as vitamin K. Other, high potential substances have not been used because the EFSA had not approved it for use as a food ingredient or additive due to lack of safety information, such as in the case of benfotiamine. A lot of the ingredients function using antioxidant-working mechanisms. When developing these supplements, especially the microvascular tablet promoting kidney and eye health, it was assumed that the antioxidant theory is realistic and beneficial for human health based on the available literature. **Claims:** Every food supplement holds at least one relevant health claim. Vitamin B₂, riboflavin, has no direct link with diabetic retinopathy, but in contrast to the other ingredients in the eye-tablet, a health claim regarding maintenance of normal vision is approved by EFSA. **Manufacturability:** Almost all food supplements met the minimal or maximal requirements set for friability, hardness and disintegration, the latter with the exception of the memory tablet. If the disintegration time of a tablet is too long, the tablet will not disintegrate in the stomach, and therefore the content cannot be absorbed properly. To reduce the disintegration time a disintegration agent will be added which is soluble in water and will loosen the binding of the tablet and therefore decrease the disintegration time of the tablets. The mood tablet scored a mean hardness of 78 N, while 80 N was recommended. The hardness of a tablet is important to ensure the quality of the tablet during the production and the logistic process from manufacturer to consumer. The hardness is however not as important as the friability, weight and thickness. Therefore, in this case where the deviation is minor, no changes in excipients will be made. **Other aspects:** Also affordability and the market competition were taken into account when designing this range of food supplements. **Limitations:** Notwithstanding that this product line was designed with the best intentions, there are some limitations which should actually be considered. For instance, the bioavailability of the ingredients and interactions between nutrients is not taken into account. Especially when several different supplements are taken simultaneously, interactions can become

a major factor in the efficiency of absorption, bioavailability and mechanism of action (13)F. Several herbal extracts were used in this food supplement range. Problems with these extract could occur when extracts of low quality (fluctuating amounts of active ingredients) are used (14). A solution is to choose standardised herbal extracts. In addition, quality control on every batch has to be done (15). Moreover, type 2 diabetes is common in the elderly population (16). Elderly frequently take several medicines and experience difficulties swallowing tablets (17). The tablets of this product line are rather big. An improvement could be to divide the doses over several smaller tablets.

Conclusion

The food supplements as stated above, meet all the requirements set to develop a proper food supplement for type 2 diabetics, regarding both technological and biomedical aspects. Also, marketing and sales aspects were a major feature in the development of the food supplements. Hence, several ingredients have been rejected. What should be taken into account to optimise the tablets is the bioavailability of the ingredients. Also the interactions in-between nutrients have not been considered in these supplement range. In addition, the target population should be portrayed better and considered when designing the food supplements.



Role of the student

Linde Rademakers was an undergraduate student in Biomedical Science working under the supervision of Prof. Dr. Aalt Bast from the department of Toxicology. This research in this report was performed at Herkel bv. in Zeewolde.

References

1. International Diabetes Federation. The IDF Diabetes Atlas Brussels2013. 5th [Available from: <http://www.idf.org/diabetesatlas/data-visualisations>].
2. Volksgezondheid Toekomst Verkenning. Nationaal Kompas Volksgezondheid Bilthoven, NL2014. 4.17:[Available from: <http://www.nationaalkompas.nl/>].
3. Williams textbook of endocrinology. 12th ed. Philadelphia: Elsevier/Saunders.
4. Shoback. Greenspan's basic & clinical endocrinology 9th ed. New York: McGraw-Hill Medical2011.
5. Oguntibeju OO. Pathophysiology and Complications of Diabetes Mellitus: InTech; 2012. 136 p.
6. Folli F, Corradi D, Fanti P, Davalli A, Paez A, Giaccari A, et al. The Role of Oxidative Stress in the Pathogenesis of Type 2 Diabetes Mellitus Micro- and Macrovascular Complications: Avenues for a Mechanistic-Based Therapeutic Approach. *Current Diabetes Reviews*. 2011 //;7(5):313-24.
7. Dutch Diabetes Federation. Voedingsrichtlijn voor diabetes type 1 en 2 mersfoort2010. Available from: <http://www.apotheekkennisbank.nl/sites/default/files/content/link/uploads/NDF-Voedingsrichtlijn2010.pdf>.
8. Koga M, Kasayama S. Clinical impact of glycated albumin as another glycemic control marker. *Endocrine journal*. 2010;57(9):751-62. PubMed PMID: 20724796. Epub 2010/08/21. eng.
9. Puddu A, Viviani GL. Advanced glycation endproducts and diabetes. Beyond vascular complications. *Endocrine, metabolic & immune disorders drug targets*. 2011 Jun;11(2):132-40. PubMed PMID: 21476962. Epub 2011/04/12. eng.
10. EU Register on Nutrition and health claims [Internet]. [cited 14 April 2014]. Available from: <http://ec.europa.eu/nuhclaims/?event=search&CFID=1163301&CFTOKEN=70fb753c637cfc2a-FB40E170-C862-CE5F-8431281B61519C9F&jsessionid=9212356a9ca37d8e894c50162e7b5b177fb4TR>.
11. Council EPat. C1 Regulation (EC) No. 1924/2006 on nutrition and health claims made on foods 2006. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:2006R1924:20080304:EN:PDF>.
12. EU. COMMISSION DIRECTIVE 2008/100/EC 2008. Directives on nutritional labelling for foodstuffs as regards recommended daily allowances, energy conversion factors and definitions]. Available from: <http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2008:285:0009:0012:EN:PDF>.
13. Holst B, Williamson G. Nutrients and phytochemicals: from bioavailability to bioefficacy beyond antioxidants. *Current opinion in biotechnology*. 2008;19(2):73-82.
14. Linde K, Mulrow C, Berner M, Egger M. St John's wort for depression. *The Cochrane Library*. 2005.
15. Schilter B, Andersson C, Anton R, Constable A, Kleiner J, O'Brien J, et al. Guidance for the safety assessment of botanicals and botanical preparations for use in food and food supplements. *Food and Chemical Toxicology*. 2003;41(12):1625-49.
16. Meneilly GS, Tessier D. Diabetes in elderly adults. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*. 2001;56(1):M5-M13.
17. Schindler JS, Kelly JH. Swallowing disorders in the elderly. *The Laryngoscope*. 2002;112(4):589-602.