

Review Article

ORAL VIAL WITH PLUNGER AND TEAR OFF CAP (VPTC) IS AN ALTERNATIVE DOSAGE FORM FOR DIETARY SUPPLEMENTS

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ABSTRACT

"Oral vial with plunger and tear off cap" (VPTC) is introduced as a novel dosage form to combine the advantages of liquid dosages with those of solid dosages and to ensure the quality of the product at the time of administration. It is ideal for minerals, vitamins, plant extracts, proteins, amino acids, prebiotics and probiotics. This present review highlights the advantages of the dosage form VPTC, a full description of it, formulation development, some marketed preparations and some common designs of dispensing caps in the world.

Keywords: Dispensing cap, Dietary supplement, VPTC, Tear off cap, Oral vial, Smart Delivery Cap

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INTRODUCTION

The simple and easy way of administration of the drug is through the oral route. Oral intake is the most suitable and frequently employed route of drug delivery owing to its ease of administration, high patient compliance, cost effectiveness, least sterility constraints, and flexibility in the design of dosage form [1-4]. Liquid dosage forms are useful for a number of reasons like ability to be administered to children or people unable to swallow tablets or capsules [5]. "Oral vial with plunger and tear off cap" (VPTC) is designed specially to combine the advantages of liquid dosages with those of solid dosages. Dietary supplements include such ingredients as vitamins, minerals, herbs, amino acids, and enzymes. Dietary supplements are marketed in forms such as tablets, capsules, soft gels, gel caps, powders, and liquids [6]. Vitamins and minerals are commonly used as dietary supplements to promote health and prevent chronic diseases [7, 8]. In the National Health and Nutrition Examination Survey III (1988–1994), nearly half of the U. S. population reported using a dietary supplement. A "multivitamin" was the most frequently used supplement [9]. Americans spend an estimated \$11.8 billion each year on vitamin and mineral supplements [10]. Probiotics are defined as "live microorganisms which, when administered in adequate amounts, confer a health benefit on the host" according to the consensus of a multinational expert group of scientists convened in 2001 by the Food and Agriculture Organization of the United Nations (FAO) [11]. The term symbiotic refers to a product that contains both probiotics and prebiotics [12]. Probiotics have been extensively studied and explored commercially in many different products in the world. Recent studies have suggested that probiotics have demonstrated beneficial effects to human and animal health. Much of the clinical probiotic research has been aimed at infantile, antibiotic-related and traveller's diarrhea. The non-pathogenic organisms used as probiotics consist of a wide variety of species and subspecies, and the ability to adhere, colonise and modulate the human gastrointestinal system is not a universal property. *Lactobacillus* and *Bifidobacterium* are the main probiotic groups; however, there are reports on the probiotic potential of yeasts. Some of the identified probiotic strains exhibit anti-inflammatory, anti-allergic and other important properties. Besides, the consumption of dairy and non-dairy products stimulates the immunity in different ways [13]. Colonic foods, which encourage the growth of favourable bacteria, are referred to as prebiotics. Oligosaccharides such as lactulose, galactooligosaccharides, inulin, fructooligosaccharides, and other food carbohydrates are some of the well-known examples of prebiotics. There is an obvious potential for a synergetic effect when

combining probiotics and prebiotics appropriately because prebiotics promotes the growth and activities of probiotics. By increasing the amount of prebiotics in the diet, it is possible to increase and maintain healthy bacterial gut flora in the host [14, 15]. The main aim of this work is to review the advantages of the dosage form VPTC, a full description of it, formulation development, some marketed preparations and some common designs of dispensing caps in the world.

Description of the dosage form (VPTC)

Oral vial with plunger and tear off cap is a dosage form consists of a dispensing cap and single-dose oral vial. The dispensing cap includes two caps, a reservoir cap which stores liquid (in some designs) or dry substances and tears off cap. The single-dose oral vial contains a liquid which is prepared specially to dissolve/or suspend the content of the reservoir cap or to be miscible with it. This dosage form allows the use of drugs, dietary supplements and probiotics that would discolour, degrade or interact with other substances when added to the contents of the vial, to remain stable and/or inactive until the time of use. Use the dosage form as shown in fig. 1, remove plastic cap, then press (push) the plunger into the vial shaking well then drink the whole solution or dilute it in another liquid. plunger in this design has two roles, first: as a reservoir cap to preserve active ingredients in it, second: a tool to push the ingredients into the vial through tear off cap. Humana Pharma International has developed innovative patented technology: SDC® (Smart Delivery Cap), involves as shown in fig. 2, twist and shake rather than a push. VPTC can contain and preserve generally up to 350 mg of active and inactive ingredients in the reservoir cap. in addition, some stable and active ingredients may be added to the liquid of the single-dose oral vial [16, 17].

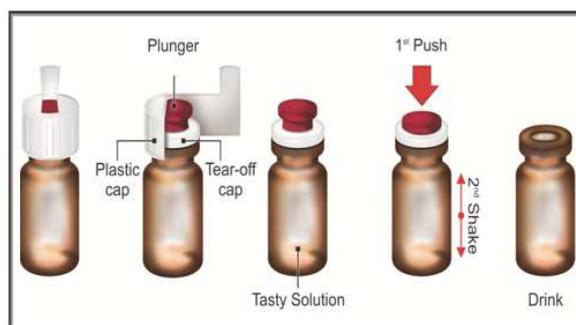


Fig. 1: How to use the dosage form [16]

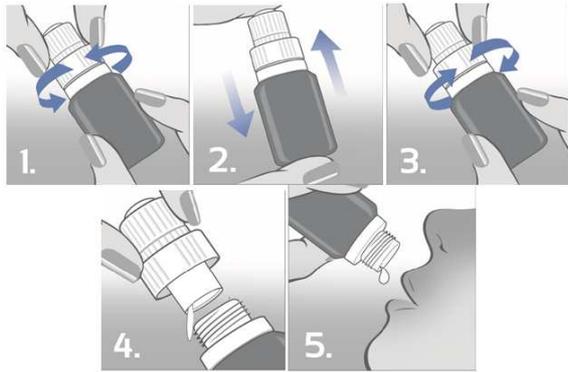


Fig. 2: SDC® technology [17]

Advantages of the dosage form VPTC

VPTC is a dosage form that combines advantages of liquid dosages with those of solid dosages. it is suitable for patients who have trouble swallowing; it also has accurate dosing and good stability, it is a single-dose product, so no need to measure the dose. It is ideally

suitable to formulations that are not possible to present in the dosage form "oral solution" due to many reasons like stability. VPTC has fast absorption because medications and dietary supplements in this dosage form are dissolved or are present in small particles suspended in a vehicle so they can be readily absorbed into the bloodstream. It ensures the quality of the product at the time that will be administered. VPTC has small size and light weight, and it may be presented as sugar-free [18]. The FDA defines the label "Sugar-Free " as a claim that may be used on food that contains Less than 0.5 g sugars per RACC(Reference amounts customarily consumed) and per labelled serving [19].

Dispensing caps

A dispensing cap or "functional cap" is a cap that is suitable for use in combination with a liquid container such as vial, can, bag, plastic or glass bottle. It is used to store and preserve liquid or dry substances separately from the liquid in which they are released to form healthy or medicinal drinks. It allows the use of drugs, dietary supplements and probiotics that would discolor, degrade or interact with other substances when added to the contents of the container, to remain stable and/or inactive until the time of use. Therefore, many healthy beverages and nutrients are currently sold without the added beneficial ingredients [20]. Table 1 shows top specifications of some of the most common dispensing caps in the world.

Table 1: Some of the most common dispensing caps in the world

| Dispensing Cap | Manufacturer | Specifications | Image | Reference | | | | | | | | | | | | | | | | | | | | | | | | |
|------------------|---|---|--|---------------|--------------------|----------------|--|--------------------|------------------------------|------------------------------|------------------|---|----------------------|--|----------------|-----|-----|-----|---------------|---|---|---|------------------|--|------------------------------------|---|--|------|
| LifeTop® | BERICAP and BioGaia | <ul style="list-style-type: none"> a plastic screw closure to be used on standard neck finishes (30/25, 38 mm, etc...). an aluminium barrier blister containing the ingredients up to 200 µl in liquid form or 200 mg in powder is sealed inside the plastic closure and offering a unique solution against humidity, which is supporting a long shelf life of the sensitive ingredients. a flexible dome, protected by a hinged overcap that is used to press on the blister, to tear off the lower part of the blister and to deliver the ingredients into the liquid in the bottle. Ingredients can be vitamins, minerals, freeze-dried probiotics, colouring agents, aromas, trace elements and carriers. | | [21] | | | | | | | | | | | | | | | | | | | | | | | | |
| Cedevita cap® | Teamplast | <ul style="list-style-type: none"> One simple rotating movement will break the seal. Cedevita Go! (a popular vitamin drink from Croatia) | | [22] | | | | | | | | | | | | | | | | | | | | | | | | |
| Power Cap® | Liquid Health Labs | <p>Three Designs</p> <table border="1"> <thead> <tr> <th>Design</th> <th>PowerCap-Push</th> <th>PowerCap-Universal</th> <th>PowerCap-Twist</th> </tr> </thead> <tbody> <tr> <td></td> <td>28 mm,38 mm, 43 mm</td> <td>26.7 mm, 28 mm, 30 mm, 43 mm</td> <td>26.7 mm, 28 mm, 30 mm, 43 mm</td> </tr> <tr> <td>Benefit s</td> <td>Fitness Cap sleek, slender and easy to Push</td> <td>On the go technology</td> <td>Includes Sports Cap Easy to twist, large load capacity</td> </tr> <tr> <td>Chamber</td> <td>6cc</td> <td>4cc</td> <td>5cc</td> </tr> <tr> <td>Pieces</td> <td>2</td> <td>2</td> <td>2</td> </tr> <tr> <td>Adaptable</td> <td>Designed to fit on existing bottling lines</td> <td>One-of-a-kind adapts to any bottle</td> <td>Designed to fit existing bottling lines</td> </tr> </tbody> </table> | Design | PowerCap-Push | PowerCap-Universal | PowerCap-Twist | | 28 mm,38 mm, 43 mm | 26.7 mm, 28 mm, 30 mm, 43 mm | 26.7 mm, 28 mm, 30 mm, 43 mm | Benefit s | Fitness Cap sleek, slender and easy to Push | On the go technology | Includes Sports Cap Easy to twist, large load capacity | Chamber | 6cc | 4cc | 5cc | Pieces | 2 | 2 | 2 | Adaptable | Designed to fit on existing bottling lines | One-of-a-kind adapts to any bottle | Designed to fit existing bottling lines | | [23] |
| Design | PowerCap-Push | PowerCap-Universal | PowerCap-Twist | | | | | | | | | | | | | | | | | | | | | | | | | |
| | 28 mm,38 mm, 43 mm | 26.7 mm, 28 mm, 30 mm, 43 mm | 26.7 mm, 28 mm, 30 mm, 43 mm | | | | | | | | | | | | | | | | | | | | | | | | | |
| Benefit s | Fitness Cap sleek, slender and easy to Push | On the go technology | Includes Sports Cap Easy to twist, large load capacity | | | | | | | | | | | | | | | | | | | | | | | | | |
| Chamber | 6cc | 4cc | 5cc | | | | | | | | | | | | | | | | | | | | | | | | | |
| Pieces | 2 | 2 | 2 | | | | | | | | | | | | | | | | | | | | | | | | | |
| Adaptable | Designed to fit on existing bottling lines | One-of-a-kind adapts to any bottle | Designed to fit existing bottling lines | | | | | | | | | | | | | | | | | | | | | | | | | |
| ViCap | Vicapystems Ltd | <ul style="list-style-type: none"> ViCap looks like a conventional sports cap. It contains a chamber which can discharge 12.5 millilitres of liquid concentrate or 7 grams of powder to create a flavoured drink out of a bottle of water. It can also be used to add a nutritional supplement or in a whole host of other applications such as hair dyes. | | [24] | | | | | | | | | | | | | | | | | | | | | | | | |
| Shinsen™Cap | Fresh Beverages International | <ul style="list-style-type: none"> Superior light, oxygen and moisture barriers, patented seal and " nitrogen gas flushing", addresses off-notes or tastes, stability challenges and oxidative. Proven stability for Probiotics. Proven suitability for nutraceutical, hygroscopic and water-soluble ingredients—eg. Co-enzyme Q10, polyphenols, catechin, 16 mo on green tea, commercially available in Japan. | | [25] | | | | | | | | | | | | | | | | | | | | | | | | |

Tab the cap "Single-serve cap"[™]

Tap the Cap, as shown in fig. 3, is a dispensing cap which is "stand-alone". It can fit any water bottle worldwide with a diameter between 26 mm–32 mm, so the consumer can stay loyal to his favourite brand of bottle water and can have "health-on-the-go" [26].



Fig. 3: Tap the Cap [26]

Formulation development

In 2014 Ruba kello has developed a new sugar-free formulation of vitamins C, E, B6 and minerals Zn²⁺ and Mn²⁺ for children in the dosage form "oral vial with the plunger and tear off cap". Ingredients of the Formulation I as showed in table 2 in the dispensing cap: soluble and insoluble vitamins with minerals, mannitol as a filler, sucrose as a binding agent and sodium benzoate as an antimicrobial preservative. granules were prepared by means of wet granulation method, and the granulator consisted of alcohol and water (80:20). In the vial: Sorbitol 70% as sweetening agent and vehicle in the formulation, Glycerin as viscosity increasing agent, Acesulfame potassium as sweetening agent, Sodium benzoate as antimicrobial preservative, citric acid monohydrate and sodium citrate as buffering agent, Vanillin powder, peppermint oil and strawberry liquid as flavoring agent, polysorbate 80 is nonionic surfactant it was used as solubilizing agent for vitamin E because it is oil soluble vitamin. PEG 6000 was used to enhance the aqueous solubility or dissolution characterization of vitamin E by making solid dispersions. Product in its final form was evaluated for many parameters like appearance, Loss on drying for the granulated part, pH for solution part and assay [18]. The formulation was subjected to stability studies as per ICH guidelines at temperatures and

humidity of 40 °C/75% RH±5% RH for six months [27]. Results of stability studies for all vitamins and minerals were found within the limits but there was a significant change in assay of vitamins C and B6; in addition, there was failure in meeting the acceptance criteria for color of the granulated part. So additional testing at the intermediate storage condition 30 °C/65% RH±5% RH " If long-term studies were conducted at 25 °C/60% RH±5% RH " should be conducted and evaluated against significant change criteria [18]. In 2015 Ruba kello has developed a new sugar free formulation of ferrous gluconate in oral vial with plunger and tear off cap (VPTC). Ingredients of the Formulation II as shown in table 3, In the Dispensing cap: ferrous gluconate as active ingredient, it was included in this part to get the maximum stability and to present the product as sugar free solution because aqueous solutions of ferrous gluconate are stabilized by the addition of glucose [16, 28]. so the separation between ferrous gluconate in a plunger and the solution in a vial then dissolve it by pressing the plunger into the vial through tear off cap just before taking the medicine is the best choice to get stable and sugar free solution product. In the vial: Sorbitol 70% as sweetening agent and vehicle in the formulation, Glycerin as viscosity increasing agent and cosolvent, sucralose as sweetening agent, Sodium benzoate as antimicrobial preservative, citric acid monohydrate and sodium citrate as buffering agent, soluble caramel color as coloring agent, vanillin powder, peppermint oil and Strawberry flavor as flavoring agent [16]. Ferrous gluconate is freely but slowly soluble in water [29], and to overcome the problem of slow solubility of it in water, glycerin was used as cosolvent. Because ferrous gluconate is soluble in glycerin [30].

Oxidation of ferrous gluconate solutions is retarded and stability improved by buffering to pH of 3.5 to 4.5 with citrate buffer. This value was considered although the contact time between ferrous gluconate in the plunger and solution in the vial is very short but the value was chosen to be 3.5-4.0 to get a tasty taste and to present the product in optimal specifications. An amber vial was used to protect ferrous gluconate in the tear-off cap and plunger completely from light because ferrous gluconate is affected by light [31]. Product in its final form was evaluated for many parameters like appearance, pH of solution part and assay. Results of all tests were found within limits. VPTC can contain and some preserve generally up to 350 mg of active and inactive ingredients in the reservoir cap. in addition, stable and active ingredients may be added to the liquid of the single-dose oral vial at adjusted pH such as taurine; which is a semi-essential amino acid that is found in many tissues and is especially important for the function of skeletal muscle [32-36]; to decrease the capacity load of the dispensing caps.

Table 2: Ingredients of the formulation I

| In the plunger | | | |
|-------------------------|-----------------------------|------------------------|------------------------|
| Ingredients | theoretical amounts mg/unit | Actual amounts mg/unit | Actual amounts g/batch |
| Vitamin C* | 45.00 | 63.00 (overage 40%) | 94.50 |
| Vitamin E 50%* | 7.50 | 22.16 (overage 50 %) | 33.24 |
| Vitamin B6* | 1.50 | 2.10 (overage 40%) | 3.15 |
| Zinc (ZnSO4. H2O) | 5.00 | 13.76 | 20.64 |
| Manganese (MnSO4. H2O) | 1.50 | 4.58 | 6.87 |
| Mannitol | - | 85.20 | 127.80 |
| Sucrose (grind) | - | 3.00 | 4.50 |
| Sodium Benzoate | - | 6.20 | 9.30 |
| Total | - | 200.00 mg | 300.00 g |
| In the vial | | | |
| Ingredients | Quantity per unit/g | Quantity per batch | |
| Sorbitol | 2.40000 | 720.00000 | |
| Glycerin | 1.00000 | 300.00000 | |
| Acesulfame. K | 0.01660 | 4.98000 | |
| Sodium Benzoate | 0.01880 | 0.56300 | |
| Citric acid monohydrate | 0.04120 | 12.35100 | |
| Sodium citrate | 0.00149 | 0.44700 | |
| Vanillin powder | 0.00150 | 0.45000 | |
| Peppermint oil | 0.00030 | 0.09000 | |
| Strawberry | 0.05000 | 15.00000 | |
| PEG 6000 | 0.07000 | 21.00000 | |
| Tween 80 | 0.11250 | 33.75000 | |
| Purified water | Up to 10.00000 ml | Up to 3000.00000 ml | |

*Use of an overage of a vitamin is to compensate for expected degradation during product shelf life because vitamins decompose easily.

Table 3: Ingredients of the formulation II

| In the plunger | | |
|-------------------------|---|----------------------------------|
| Ingredients | theoretical amounts mg/unit | Actual amounts mg/unit |
| Ferrous gluconate | 335.72 mg equivalent to 37.50 mg of iron (II) | 335.72+(overage 5%*) = 352.515 % |
| In the vial | | |
| Ingredients | Quantity g/unit | |
| Sorbitol 70% | 2.40000 | |
| Sucralose | 0.00500 | |
| Sodium Benzoate | 0.02500 | |
| Citric Acid monohydrate | 0.03500 Or to get the required pH | |
| Sodium Citrate | 0.00223 | |
| Vanillin powder | 0.00150 | |
| Peppermint oil | 0.00030 | |
| Strawberry liquid | 0.05000 | |
| Glycerin | 1.60000 | |
| Soluble caramel color | 0.00320 | |
| Purified water | Up to 10.00000 ml | |

* an average of ferrous gluconate was used to compensate for expected degradation during products shelf life.

Marketed preparations

Lactogèrmine plus, Lactogèrmine baby and Lactogèrmine Penta are developed by Humana Pharma International in an innovative patented technology SDC ® "Smart Delivery Cap" as shown in fig. 4. Lactogèrmine plus is a dietary supplement with probiotics, water-

soluble vitamins and prebiotics [37]. Lactogèrmine baby contains *lactobacillus rhamnosus* that promotes the balance of intestinal flora [38]. Lactogèrmine Penta is a bio-selective activator of the intestinal flora, comprising the combination of a prebiotic (galactooligosaccharides) and live lactic ferments [39]. Formulations of products are shown in tables 4. 5 and 6 respectively.

Table 4: Ingredients of lactogèrmine plus

| Ingredients | |
|--|---|
| In the cap | In the vial |
| Vitamin B1 mononitrate | Galacto-oligosaccharides (milk origin) prebiotic" |
| Vitamin B 2 | Fructose |
| Vitamin B6 hydrochloride | Preservatives E202, E211 |
| Vitamin B12 | Flavor |
| Niacinamide | Citric acid "acidity regulator." |
| Folic acid | Purified water |
| Calcium pantothenate | |
| Lactobacillus rhamnosus ATCC-53103 | |
| Saccharomyces boulardii CNCM I-3799 | |
| Mannitol | |
| Maltodextrins | |
| Anti-caking agent: magnesium stearate, silicon dioxide | |
| Bulking agent: microcrystalline cellulose | |

Table 5: Ingredients of lactogèrmine baby

| Ingredients | |
|---|---------------------|
| In the cap | In the vial |
| <i>Lactobacillus rhamnosus</i> ATCC-53103 | Flavoring agent |
| Magnesium stearate, | E306 as antioxidant |
| Silicon dioxide | Sunflower oil |
| Maltodextrins | |

Table 6: Ingredients of lactogèrmine penta

| Ingredients | |
|---|------------------------------------|
| In the cap | In the vial |
| <i>Bifidobacterium bifidum</i> | Galacto-oligosaccharides |
| <i>Lactobacillus bulgaricus</i> supported by maltodextrin | Fructose |
| <i>Streptococcus thermophilus</i> | Citric acid |
| <i>lactobacillus rhamnosus</i> supported by corn starch | Flavoring agent |
| Galacto-oligosaccharide | Potassium sorbate |
| Microcrystalline cellulose | Sodium benzoate |
| Magnesium stearate | Distilled water by reverse osmosis |
| Colloidal silicon | |
| Ascorbic acid | |

CONCLUSION

Recent and available studies have demonstrated that oral vial with plunger and tear off cap is an alternative dosage form for dietary supplements. It is ideal for minerals, water-soluble and insoluble vitamins, plant extracts, proteins, amino acids, prebiotics and probiotics. It combines the advantages of liquid dosages with those of solid dosages and ensures the quality of the product at the time that will be administered. Therefore, many healthy beverages and nutrients are currently sold without the added beneficial ingredients. With the explosion of dispensing caps in the nutrition industries, we should expect an equal explosion in the use of the dosage form VPTC in the pharmaceutical industries.

CONFLICTS OF INTERESTS

Declared none

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