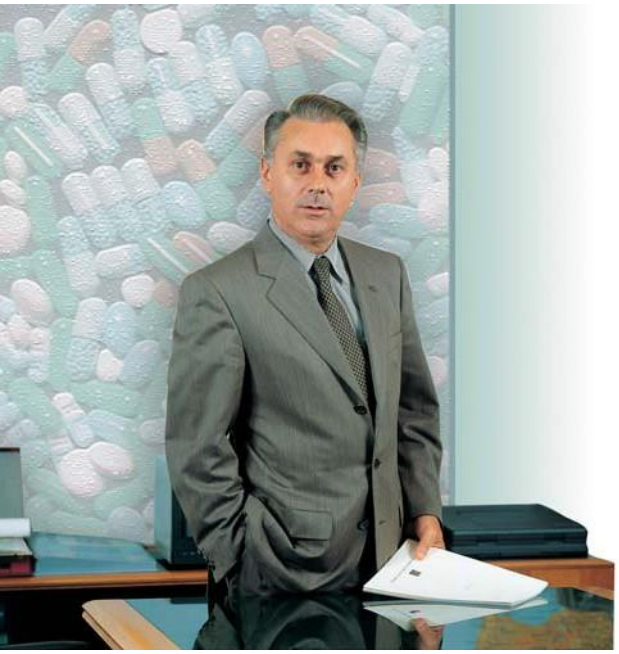
SURACTIVES®

INNOVATIVE FORMS OF FOOD SUPPLEMENTS FOR ORAL USE:

M.A.T.R.I.S.®

A NEW TECHNOLOGY

ips srl
controlled release food supplements
SURACTIVES® DIVISION

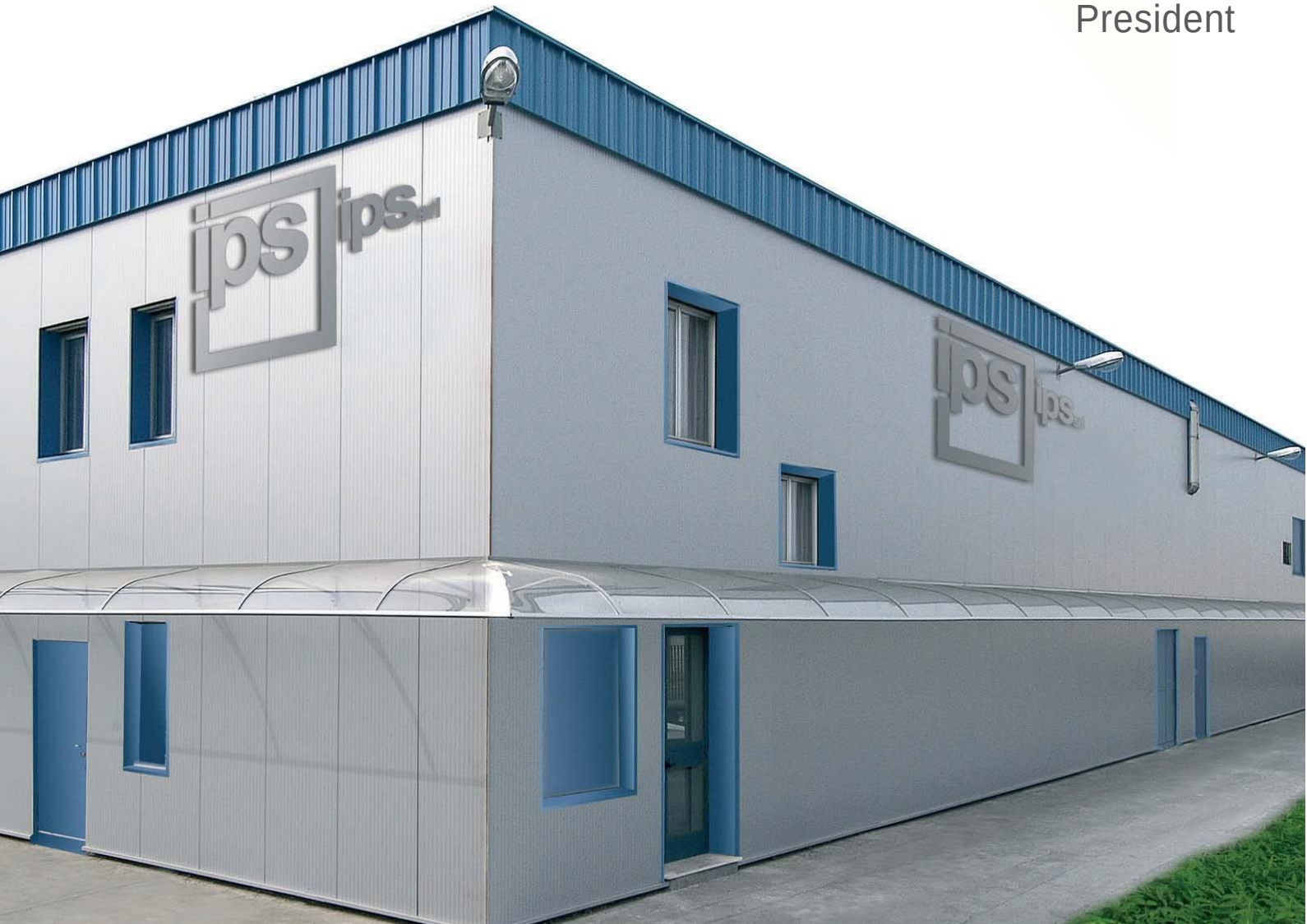


After years of experience by its technical staff in R & D of controlled-release pharmaceutical products, I.P.S. has devoted the last few years to third party industrial development and production of controlled release and taste masking food supplements, identified by the brand

SURACTIVES®

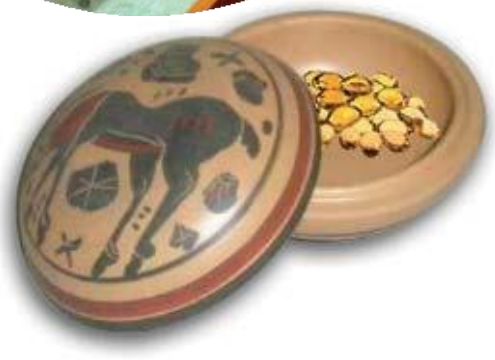
Our determination is to further improve our skills and experience,
thus reinforcing our image as
a forefront supplier of innovative products in this area.

Gino Pasotti
President



CONTROLLED RELEASE OF ACTIVE INGREDIENTS

In some tombs of Egyptian pharaohs, small gold spheres were found containing plant substances, considered actual "capsules" intended for the oral administration of substances with therapeutic activity.



This seems to show the interest since ancient times for oral forms with the purpose of prolonging the therapeutic activity of the active ingredients and thereby obtaining, with the same efficacy, a reduction in administration frequency (patient compliance).

Whilst there are legitimate doubts concerning the effectiveness of such "capsules", although presumably intended for repeated use, there is no doubt that these attempts would coincide precisely with the modern concept of controlled release of active ingredients for oral use, although at the time, and for many centuries afterwards, this would have been limited to ease of administration.

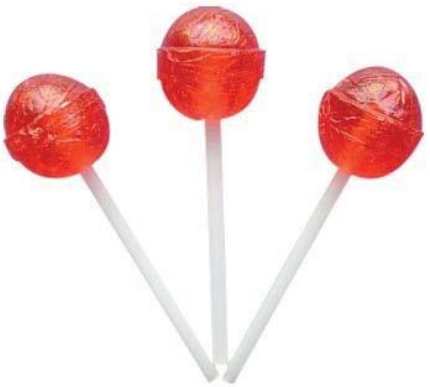
Let us briefly see the main stages of the evolution of this concept and how the idea of therapeutic controlled release ingredients has developed over the centuries right up to the latest technological achievements of our times.

FOREWORD

First and foremost it is necessary to specify that all the considerations below apply equally well to both drugs and food supplements, as the affinity of the two categories of products in terms of method of administration (oral), the behaviour of the recipient organism (metabolism) and the criteria for evaluating their therapeutic activity, is evident.

DEVELOPMENTS IN TECHNOLOGY

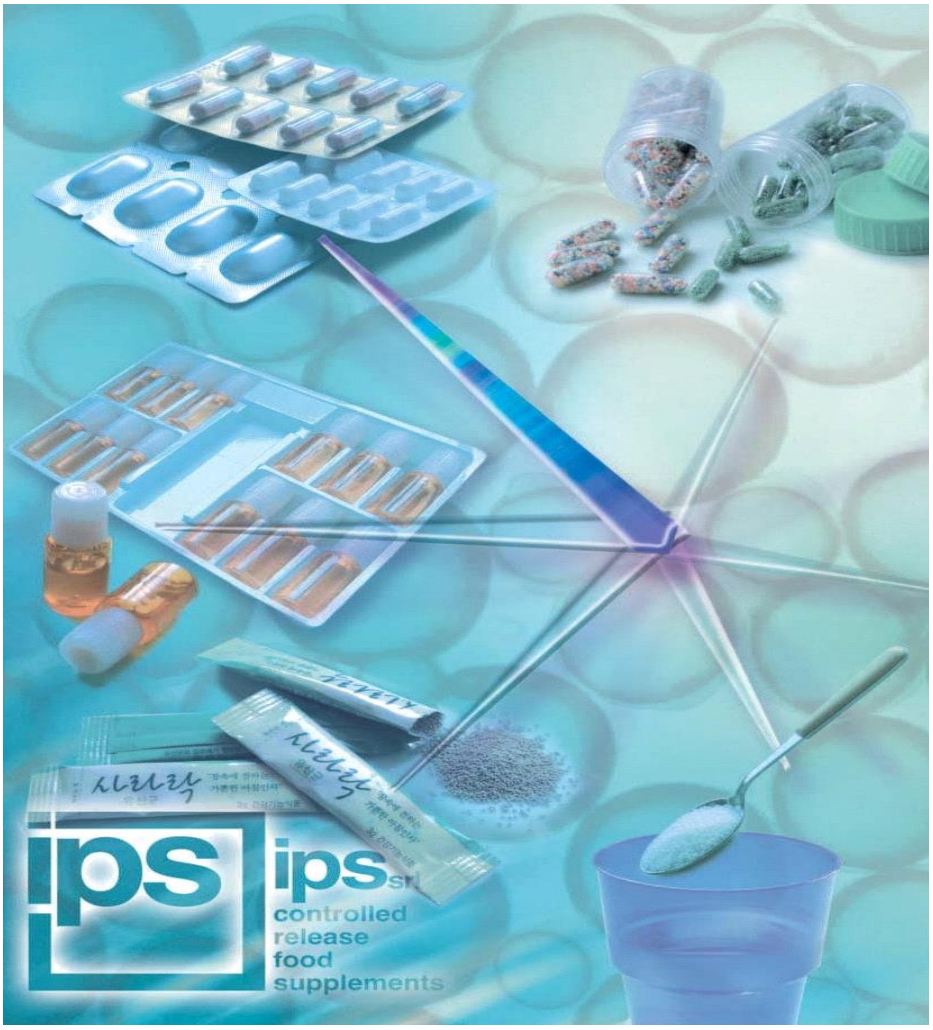
Despite several attempts over the centuries to make formulations of controlled release active ingredients in the form of tablets, pills, granules, boluses, tabloids, mucilage, cachets, right up to lollipops and medicinal chocolate products, in order to reduce the frequency of administration or for protection of gastro-sensitive substances, the study on a scientific basis only began in conjunction with two key events:



1. The birth of modern pharmacology (mid-nineteenth century) in particular of pharmacokinetics (what the body does to the drug: absorption, distribution, metabolism, excretion) and pharmaco-dynamics (what that the drug does to the body: biochemical and physiological effects of the drugs and their action mechanism).

Thanks to these branches of pharmacology, it has finally been possible to establish, among other things, the optimal characteristics of release of therapeutically active substances.

2. The discovery of suitable polymers, both natural and synthetic, designed to allow the release and absorption within the chosen gastro-intestinal tract and in the desired manner.



FUNDAMENTAL MILESTONES

CONTROLLED-RELEASE PRODUCTS BY DISSOLUTION

The first real discovery dates back to 1949, when the technician of a major US pharmaceutical industry saw a pack of small discs of chocolate covered with white granules in a supermarket. That led to the idea of filling hard gelatine capsules with neutral media in the form of granules, coated with active principles able to dissolve at different time intervals, thanks to a membrane coating of the granules themselves, with a more or less rapid dissolution based on different thicknesses.

This invention made it possible to quickly obtain the release of an initial dose of active ingredient (active uncovered granules), with the subsequent gradual release of small doses (thicker membrane granules) thus maintaining the therapeutic level for 8-10 hours, with undoubted increased comfort and safer use (patient compliance).

The first drug in this form was launched on the American market in 1952.

The discovery, besides contributing to an easier acceptance of the proposed therapy, also had other important advantages, actually more the result of randomness (Serendipity) than of real research. In particular, a lower toxicity level of the active ingredients compared with conventional dosage forms, thanks to dividing the total dose into numerous micro-doses (active granules) and therefore obtaining a reduced concentration in a specific point of the body, with fewer side-effects.

However this formulation presented some drawbacks, the main one of which was the randomness of the release, due to the unpredictable speed of disintegration of the membrane, since this depends on a number of physiological variables which differ from individual to individual, and even in the same individual at different times, such as gastro-intestinal motility, pH, amount of fluids, the presence or absence of food.

Furthermore, a limited capacity of the capsules and swallowing difficulties, especially for geriatric and paediatric products.

CONTROLLED-RELEASE PRODUCTS BY DIFFUSION

In the early 60s, the discovery of a new and advanced form of release, still in the United States and in granules for hard gelatine capsules, was made possible by the availability of new polymers for the diffusion of the active ingredients they contained, instead of the dissolution of the membrane coating.

In this case, an insoluble and permeable membrane is used, which allows the entry of body fluids through its pores and the leakage of the active principle by diffusion, a phenomenon largely independent from the physiological variables indicated above.

A much more reliable release of the active ingredient became possible with this technology, but the drawbacks mentioned above remained: hard gelatine capsules, virtually the only possible dosage form, their limited capacity and the swallowing difficulties.

OSMOTIC PUMP

The development of research in the field of controlled-release drugs for oral use, at the end of the 80s subsequently led to the invention of drugs in the form of an osmotic pump, both for tablets and capsules: the first suitable for extended release formulations, the second for delayed or repeated release formulations.

In this case, the drug is mixed with an excipient (a water-soluble polymer) which constitutes the inner part of the system. The wall coating consists of an insoluble and semipermeable polymer membrane, in which a small hole is made with a laser.
The physiological fluids spread within the system through the membrane, forming a concentrated solution.
The concentration difference between the inside and the outside of the system generates the leakage of the active ingredient from the hole.

The advantage of a more rational bioavailability of the active ingredient is accompanied by the usual limitation features of the previous systems in this case also.

FINAL CONSIDERATIONS AND STATE OF THE ART TECHNOLOGY OF CONTROLLED-RELEASE PRODUCTS.

Recalling the above and considering that the disadvantage due to the limited capacity of hard gelatine capsules and osmotic tablets is particularly relevant when administering food supplements, normally in higher doses than those of drugs, it is possible to try to set up a dosage form that maintains all the positive aspects already seen without showing the negative aspects of the forms indicated above.

This form exists and is the result of years of research and trials by I.P.S:

M.A.T.R.I.S.®

Multiform Administration Timed Release Ingredients System

(Single system for the administration of active controlled-release ingredients in different oral forms)

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Multiform Administration Timed Release Ingredients System

This technology is based on covering each particle of active principle, sized between 200 and 800 µ, with an insoluble and permeable membrane, acting by diffusion, without any use of inactive materials.

The characteristics of this technology, which represents the state of the art in the field of oral time-released active ingredients, are the following:

1. A homogeneous and maximum dispersion of the active ingredient over the whole area of the gastrointestinal tract, for a uniform absorption during the arranged period of time.

2. Continuous release of the active ingredient by diffusion, calibrated over 8 - 10 hours, with a lower risk of local irritation and of possible unwanted side effects.

3. The possibility of gastro-resistant dosage forms.

4. The implementation of various forms of administration, such as: single dose dispersible and orosoluble sachets, single dose small bottles with dosing cap, highly soluble tablets, as well as capsules and tablets in traditional form.

5. M.A.T.R.I.S. SmarTTabs®: this type of MATRIS® tablet, developed by IPS thanks to a unique technology, deserves particular interest.

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6. High dosage per single administration, through a high title (> 80%) of the finished product in MATRIS® form, up to several grams per unit dose of the active ingredients including different ones (in single-dose sachets).

7. Total masking of the unpleasant taste of some substances.

8. Elimination of swallowing problems.

9. Modern and attractive dosage form, easy to use, for improved adherence to the proposed treatment.

The preferred and most modern form made possible by this technology is that of single-dose sachets, orosoluble or dispersible, of which numerous MATRIS® preparation forms are available on the market.

As an example, thioctic acid (or alpha-lipoic acid) suitable for the production, amongst other dosage forms, of single-dose MATRIS® form sachets up to 800 mg. per unit dose, either as taste masked (fast) or as time-release (retard).

The MATRIS® form of this supplement has a titre of 800 mg/g, is perfectly tasteless and, in the retard form, gradually releases the active principle up to eight/ten hours after ingestion.

The duration of the release, in its final form, can be varied on the basis of the ratio between the immediate release product and the time release one.

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