Review Article on Superdisintegrants Agents Used in Formulations of Sublingual Tablets

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ABSTRACT

Sublingual route of medications is preferred as it easy for patients including old people and children. In addition, it provide quick action and escaping first pass effect of liver when compared with conventional oral tablets because the drug is absorbed through blood vessels located sublingually which are numerous and saliva is efficient for rapid disintegration of sublingual tablets. Therefore, superdisintegrants are used to disintegrate rapidly. In the formulation of pills, many compounds are added, aiming to break the tablets into fine particles when water reaches them, which results in the drug being released quickly. Good disintegrates have a superior ability to act opposing the effectiveness of tablet binding materials and compressive forces to form the tablet. Sublingual tablet manufacturing targets the release of the drug in the mouth and gastrointestinal tract within a few seconds after swallowing. Therefore, the characteristics of Superdisintegrants used are important to be chosen correctly.

الخلاصة

يعتبر استخدام الادوية تحت اللسان مفضلا لأنه سهل للمرضى بما في ذلك كبار السن والأطفال. بالإضافة إلى ذلك ، فإنه يوفر مفعولًا سريعًا ويهرب من تأثير المرور الأول للكبد عند مقارنته بأقراص الفم التقليدية لأن الدواء يتم امتصاصه من خلال الأوعية الدموية الموجودة تحت اللسان والتي تكون عديدة واللعاب فعال في التفكك السريع للأقراص تحت اللسان. لذلك ، يتم استخدام المتفككين الفائقين للتفكك بسرعة. في تركيبة الحبوب ، يتم إضافة العديد من المركبات ، بهدف تفتيت الأقراص إلى جزيئات دقيقة عندما يصل الماء إليها ، مما يؤدي إلى إطلاق الدواء بسرعة. تتمتع التفككات الجيدة بقدرة فائقة على العمل ضد فعالية مواد ربط الأقراص وقوى الضغط لتشكيل الجهاز اللوحي. يستهدف تصنيع الأقراص تحت اللسان إطلاق الدواء في الفم والجهاز الهضمي في غضون ثوانٍ قليلة بعد البلع. لذلك ، من المهم أن يتم اختيار خصائص المتفككين الفائقين بشكل صحيح.

Introduction;

The way of formulating drugs into pills or sublingual liquids is a promising way, especially for the types of drugs for which oral use is limited because of hepatic first-pass metabolism [1,2]. Moreover, this path is characterized by the rapid starting of the effectiveness of the drug due to the abundant blood vessels available there, besides, the wide acceptance and ease by patients. However, there are limitations, especially in the issue of the small size of the drug. The sublingual route is problematic with low water-soluble drugs because it prevents the drug from being swallowed before being dissolved and absorbed into the sublingual membranes. We can make the sublingual pills rapidly degrade by adding superdisintegrants, with the result that the formula degrades in less than a minute in the sublingual cavity upon contact with saliva. [3].

After dissolving the pill under the tongue, the process of quickly dissolving the drug in the saliva should be achieved, and there are many techniques and methods that are used to improve the solubility of these poorly soluble drugs, such as following the complexation or solid absorption [4]. In the buccal cavity, the sublingual area is one of the most permeable areas for drug absorption, due to the abundant availability of blood vessels there, and this of course directly helps to avoid hepatic drug metabolism. This, of course, results in a high bioavailability within the body of the drug and the subsequent rapid, complete and high pharmacological efficacy with improved patient compliance [5].

In such formulations, a small amount of saliva is usually sufficient to achieve immediate disintegration and dissolution of these tablets by mouth in the oral cavity. Sublingual absorption is characterized by rapid action, but the duration of action is often short and according to the half-life of the drug [6]. This method is several times (from 3-10) greater than oral gastric route for absorption [7]. There are two types of disintegrates used in sublingual tablets which can be classified according to origin.

Types of superdisintegrants used in sublingual tablets

Synthetic superdisintegrants:

They are superdisintegrants which are fully manufactured. They are mostly used in solid dosage forms than natural ones. There are several kinds of them as follows;

Cross-linked polyvinyl-pyrrolido (Crospovidone, Polyplasdone XL, XL10)

Crospovidone is one of the commonly used polymers. It is a white powder that does not dissolve in water. With its presence, saliva enters the pill and it wicks saliva resulting in volume expansion and generation of hydrostatic pressure required for rapid disintegration under the tongue in the mouth. Crospovidone has the property of relying on a mixture of swelling and wicking. Crospovidone particles appear as granular and highly porous when examined with an electron microscope. Crospovidone has a unique shape of the porous particles which felicitate wicking of liquids into the tablets and rapid disintegration [8,9,10]. Crospovidone has a high crosslinking density so it swells quickly in water without turning it into a gel. Unlike, other super-disintegrates which are characterized by having a lower crosslinking density and as a result you find them to be a gel when they are completely hydrated[9,10].

Croscarmellose Sodium [Ac-Di-Sol]:

A white or gray-white powder that does not dissolve in water, but quickly expands to several times the original volume (from 4 to z times) and practically also does not dissolve in ethanol. hygroscopic. Croscarmellose is an internally bonded polymer of sodium carboxymethylcellulose. Croscarmellose has a high ability to swell with less gelling, which results in rapid disintegration and this is an aspiration when preparing sublingual pills. Because of the fibrous structure, croscarmellose particles have also been shown to exhibit a wicking effect. Croscarmellose sodium can be used in the preparation of tablets in both direct pressing or wet granulation processes.

It should be noted that when used in wet granulation, the addition of croscarmellose sodium should be in both the wet and dry preparation stages of the process (inside and outside the granules) so that the use of wicking and swelling capacity is achieved together. [11, 12]

Sodium Starch Glycolate (Explotab):

Sodium starch glycolate is a fine, white, free-flowing powder. It is the sodium salt of the carboxymethyl ether of starch. It has a great pharmaceutical benefit and is a modified potato starch by the crosslinking method and has the advantage that it gives good disintegrating properties. One of the main factors in determining the effect and efficiency of this polymer as a superdisintegrator is the degree of crosslinking and substitution. The crosslinking process reduces the dissolved fraction in water, viscosity during dispersion in water. Swelling of dried natural starch in water ranges from 10 to 20 percent. While this percentage increases to reach 2-3 times the original volume in modified starch when dissolving in water and the understanding of the mechanism by which this is done is the rapid absorption of water, which in turn leads to a massive increase in the size of the granules, resulting in the desired goal of rapid and homogeneous disintegration. These materials are made by introducing large hydrophilic carboxymethyl groups, in the presence of which results in disruption of the hydrogen bonds within the original structure of the polymer. As a result, water is allowed to penetrate the molecules and the polymer becomes rapidly soluble in cold water [13].

There are many researchers who apply synthetic Superdisintegrants in formulation of sublingual tablets. For instance, Alyami SH et *al* succeeded in formulation of sublingual promethazine hydrochloride tablets by direct compression using crospovidone as superdisintegrant to enhance breaking down of tablets into small particles and give fast action for relief of motion sickness [7].

Furthermore, Swapna, K. et *al* prepared loaded atenolol beads sublingual tablet using Ac-Di-Sol, crospovidone, and Explotab, which were recompressed and investigated for pre and post-compression tests proving good disintegration [14]. Also, Urvashi J et *al* prepared Tenofovir alafenamide sublingual tablets to enhance its solubility and to maximize its bioavailability using superdisintegrants crospovidone and Explotab [15]. Furthermore, Ayalasomayajula UL et *al* formulated sublingual fast disintegration tablets of rizatriptin using several superdisintegrants namely; Ac-Di-Sol, crospovidone and L-HPC. They were characterized before compression and after compression. The formulation containing crospovidone 5% was the best [16]. Similarly, Crospovidone could increase the bioavailability of Venlafaxine where Vishakha C et *al* formulated sublingual Venlafaxine hydrochloride to achieve good bioavailability by avoiding first pass effect using Crospovidone and Explotab. Vishakha C et *al* prepared and assessed seven trials (S1-S7), disintegration time values were 29 to 57 sec. the formula F-7 including Crospovidone was the best formulation [17]. On the other hand, Chitlange PR et *al* prepared Prochlorperazine maleate sublingual tablets to maximize Prochlorperazine bioavailability as the appropriate formulation was obtained by the melt granulation applying Ac-Di-Sol achieved disintegration time ranged from 20 to 190 sec [18]

Natural superdisintegrants:

Natural superdisinegrating are preferable than synthetic substances due to their nature, cheapness, availability, and non-toxicity like gums and mucilages that have been employed tremendously in drug delivery because they are available, cheap, Eco friend, emollient, degradable and compatible. [17]. There several kinds of natural superdisintegrants are discussed below:

Chitin and chitosan:

Chitin is the chief polysaccharide existing in the world after cellulose. It is of a marine source which is a basic constituent in the shells of shellfish and creepy crawlies and it is precursor of chitosan by a deacetylation which is further applied in sublingual tablets. Chitin and chitosan exhibit poor compressibility and bad bulk density. To conquer these shortcomings, they are coprecipitated in colloidal silicon dioxide to enhance their physical characteristics as well as flow characteristics which demonstrated synergistic disintegration effect. The better hygroscopic nature of chitin and silica provides a good driving force for the disintegration of fast dissolving tablets [19].

Natural gums:

A lot of types of gums occurred naturally are beneficial as superdisintegrants. For example, Guar gum originates from the endosperm of *Cyamopsis tetragonolobus* plant seeds. Guar gum is a polysaccharide made out of galactose and mannose. Gum is set up by first drying the shells in daylight, at that point physically isolating them from the seeds. The gum is industrially extricated from the seeds by sieving and cleaning techniques. Extract of gum is mainly used in the case of hypertension. Guar gum has been discovered as a good superdisintegrants because it is a natural polymer having some characteristics like it is white, insensitive to pH, and moisture.

Also, xanthan gum is derived from *Xanthomonas campestris*. It is considered a good formulation in all the delivery systems because it increases patient compliance and decreases the disintegration time than conventional delivery systems. Xanthan gum is analyzed for improving medication consistency without the disintegration of the upper layer of the drug. Xanthan gum has broad expanding properties for quicker disintegration [20].

Locust bean gum and gellan gum, karya gum has been used recently and proved to be useful as superdisintegrant [21]. Gellan gum is a polysaccharide that is created by *Pseudomonas elodea*. It is a linear, water soluble polysaccharide. Gellan gum shows gelling property in presence of mono and divalent cations. Gellan gum exhibit greater swelling ability when it comes in contact with wet environment which may be due to its highly hydrophilic nature. The disintegrant action of gum might be due to these characteristics [22, 23].

Gum Karaya is called Indian gum tragacanth, originated from genus *Sterculia* trees belonging to family sterculiaceae. Gum karaya is acidic polysaccharide containing galactose, glucuronic acid and rhamnose. Moreover, Gum karaya is highly viscous its use as a binder and disintegrant is limited in production of conventional dosage form. But if some modifications are done on gum karaya, it shows rapid disintegration of tablets. Gum karaya has low cost as it is abundantly available in nature. Also it is biocompatible so that it could be employed as a substitute superdisintegrant to other superdisintegrants [24].

Locust Bean gum is like guar gum in structure. It is taken from *Ceratonia siliqua Linn* seed endosperm which is a member of family leguminosae. The beans or brown pods of locust bean tree are milled to take locust Bean gum. The color of gum varies from white to yellowish white; it is an odorless powder. It has been investigated for bioadhesive and solubility enhancement properties. Locust Bean gum is used in pharmaceuticals as well as in food industries as a gelling, superdisintegrant and thickening agent [25, 26].

Agar:

Agar is the dehydrated coagulated material taken from red algae Gelidium mansion and a few other species. Agar is found in form of strips and coarse powders. It is colorless, odorless, and sticky. At a molecular level agar comprises two types of polysaccharides as Agarose and Agaropectin. Agarose has the great tendency of gelling agent and Agaropectin act as viscosity enhancer because of these characteristics it is used in super disintegrates tablets. It is ideal for fast disintegrating tablets just because it is inert, biodegradable, and can be used to increase the strength of the product by swelling dynamics [24].

Soy polysaccharides:

Soy polysaccharides are novel superdisintegrants used in tablet formulations by direct compression and wet granulation method. At lower concentrations, soy is more effective than starch and other polymers. In direct compression methods, soy polysaccharides exhibit parallel cross-linking with other polymers used in the formulations. Soy Polysaccharide gives promising outcomes in tablet disintegration, wetting time, and gives quicker disintegration rate. Soy polysaccharides with the commercial name of Emcosoy were employed in sublingual tablets as a superdisintegrant (4-8%) exhibiting similar effect like synthetic superdisintegrants [27,28].

Fenugreek:

Fenugreek is an herb, extracted from *Trigonella foenum* that is a member of the family of leguminous that is applied as food, nutritional additive, and traditional medicine. Fenugreek seed consists of an elevated percent of adhesive mucilage that may be exploited as a disintegration enhancer in fast dissolving tablets. It seems as a creamy yellow powder that rapidly convert to a colloid in warm water. Fenugreek mucilage has unique characteristics like quick onset of action, limited wetting time, and decreasing disintegration time of tablet. The hardness, friability, and medication substance of the apparent multitude of plans were discovered found within the limits. Improved detailing was exposed to stability according to ICH rules and its immaterial change in hardness, breaking downtime, and in vitro drug discharge [21].

Plantago ovata:

Plantago ovata is a member of family of Plantaginaceae. The fibers and mucilage exist in the plant are seeds and psyllium husk where they have elevated water absorption so, the husk swells to ten times due to existence water soluble polysaccharides that compose mucilage when added in aqueous solution. On hydrolysis, mucilage degrades into polysaccharides which have disintegrative properties [29, 30].

Many studies dealt with the usage of natural Superdisintegrants in sublingual tablets. For instance, Santhoshi et *al* formulated terbutaline sulfate sublingual tablets using natural superdisintegrants namely; karaya gum, locust bean gum and gellan gum using direct compressible technique and the best formula containing locust bean gum was chosen because it as disintegrates within 17 seconds [31]. In another study, Prajapati TS et *al* developed Sublingual zolmitriptan tablets applying ispaghula husk powder, gellan gum, sodium alginate as superdisintegrants by direct compression and characterized. The optimized formula (D5) consisting of 4% of gellan gum disintegrates within 9 seconds and all formulae exhibited 100% of dissolution within 6 min. [32]

A lot of studies investigated the usage of natural and synthetic Superdisintegrants together in the same research. Singh H et *al* developed sublingual tablet of amlodipine besylate employing natural superdisintegrants (Locust bean gum; *Plantago ovate)* and synthetic namely; Ac-Di- and Crospovidone. Rapidly dissolving tablets containing Locust bean 10% dissolved 98% of drug after 30 minutes [33].

Nishant B et *al* invented and evaluated fast dissolving sublingual tablets of Nifedipine employing natural super-disintegrant to avoid first pass. Plantago ovate was applied as a natural superdisintegrant. They employed diverse percents of synthetic and natural superdisintegrants. F9 including Plantago ovata revealed to be the best fast dissolving tablet formulation having an adequate disintegration time (40 sec.) and more than 99% of drug was dissolved in 35 min [34].

Conclusion:

The sublingual route is widely accepted by the majority of patients including geriatric and pediatric because it provides patient compliance, direct release of the drug, and ease of administration. Geriatric and pediatric patients feel inconvenience while ingesting a drug and due to this they are unable to swallow the tablet and capsule. So, the fast-dissolving tablets has proved to be a valuable invention. Many superdisintegrants are applied for quick-dissolving tablets including synthetic and natural superdisintegrants. Tablets and capsules which are presently being considered as the most preferable to administrate over other routes drug. Unfortunately they have some hindrances to patients treating with chemotherapy and patients with swallowing problem. Therefore, sublingual tablets could be acceptable delivery to expand the compliance as the percent of delivered drug and disintegration are far superior to conventional ones. Natural polymers have more dominant consequences for quick-dissolving tablets than synthetic polymers and they are non-toxic, non-irritant and biodegradable.

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