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DISINTEGRATING AGENTS THE BACKBONE OF MOUTH DISSOLVING TABLETS

Rathod. P.B[1]*, Nimbalkar. A.V[1], Jadhav. V.Y[1], Juvatkar. P.V[1], Inulkar. A.L[1], Kale. M.K[1], Kharch, A.A[1],Gokhale. S.R[2], Titkare. J.R[1], Zambare. O.M[1], Vishe. R.R[1], Thakur. S.P[1], Shinde. T.M[1], Salvi. R.R[1]

[1]Konkan Gyanpeeth Rahul Dharkar College Of Pharmacy And Research Institute, Karjat- 41020, India

[2]Ideal College of Pharmacy,Kalyan-421306, India

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Abstract:

Mouth dissolving tablets (MDT) show the quick onset of action and are currently in demand because of several advantages like palatability and a pleasant mouthfeel. MDT can be consumed without water and shows effective action in a few minutes. MDT is advantageous particularly in all groups including pediatric, mentally ill, and geriatric patients who are unable to swallow conventional tablets and capsules. Disintegrants has a significant role in quick disintegration thereby enhancing its efficacy. In presence of super disintegrants, the tablet dissolves within 5-30 seconds range. Disintegrants are classified mainly into three categories natural, synthetic, and coprocessed. Various super disintegrants e.g. croscarmellose sodium, crospovidone, and sodium starch glycolate are added in MDT for faster dissolution. Various superdisintegrants are available in the market like ludiflash, fmelt, cellactose 80, microcelac 100 and avicel DG, etc

The review describes the various formulation aspects, techniques developed for MDTs, and super disintegrants used, along with evaluation tests, drugs, marketed formulation, and various excipients used for R&D.

Keywords: *ODT, Mouth dissolving tablets, flash dose tablets, mouth disintegrating tablets, oral disintegrating tablets, super disintegrants*

Corresponding author:

Piyush Rathod,

Konkan Gyanpeeth Rahul Dharkar College of Pharmacy and Research Institute, Karjat, India,

Email id: piyushrathod2017@gmail.com

QR code

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INTRODUCTION:

The oral drug delivery system is the gold standard in the pharmaceutical industry due to its simple, secured, cheaper, and convenient mode of drug administration.[1] Among all other existing dosage forms, tablets are one of the most popular and preferable but in a few instances, tablets are not accepted by dysphagia, and pediatric patients due to their enlarged size. This drawback of tablets has been overcome by the development of a mouth dissolving drug delivery system (MDDDS) which is enriched with factors like enhanced palatability, quick onset of action, good stability, and increased bioavailability improving patient compliance drastically[2]. This fast dissolving tablet is found to disperse in less than 3 minutes[6] and thus shows a rapid onset of action. MDT is preferred majorly by pediatric and geriatric patients who face difficulty in consuming the tablet.[2] On the other side, MDT is easily accepted by traveling patients because of its ease of administration.[3] Along with fast action MDT also produces a pleasant mouthfeel after administration and thus is currently in demand. Additionally MDT which are also known as orodispersible tablets [4] has effectively hiked the business margin for the manufactures. MDT is approved by FDA in December 1996 [5] and consists of many super disintegrants e.g. croscarmellose sodium, crospovidone, and sodium starch glycolate[4] as added ingredients that help the tablets to disintegrate quickly and increase their efficacy playing an important role in the manufacturing of MDT.

In this article, we have opted to elaborate on the methods used to formulate MDT with a focus on the superdisintegrants which play a key role in the formulation of MDT. We have attempted to include details of MDT like their mode of action, different types, methods of incorporation, and their ideal properties.

This article will not only help students to inculcate their knowledge but may also help many researchers to collect information about MDT and its superdisintegrants for formulation or any other purpose.

MOUTH DISSOLVING TABLET [1] [4] [7] [8] [9] [62]

Orodispersible tablets (ODT) are placed on the tongue other than swallowing. It is easier and convenient for patients suffering from dysphagia where acquiescence is an issue and therefore an easier dosage form for patient acceptance. ODT is the type of tablets which disintegrates quickly when positioned under the tongue. For ODT, the fragmenting time differs from seconds to minutes and also depends on the size of the tablet and formulation. On the other side European pharmacopeia defines ODT as an “Uncovered tablet which disperses before ingestion in the buccal cavity”.

IDEAL PROPERTIES OF MDT

- It should be taken with water
- Should dissolve in mouth within seconds
- Must be companionable with taste making, preservatives, disintegrants, binders, and other excipients
- Must give a agreeable mouth feel
- Must leave negligible or no residue in mouth after lingual or sublingual administration.
- Must be less sensitive to surrounding conditions such as temperature and humidity

Advantages

- Elderly patient, Bedridden and stroke victim can swallow.
- MDT increases the absorption in pregastric area that is oesophagus, mouth and pharynx which provides rapid onset of action.
- Less side effects.
- It is also beneficial in some cases like motion sickness, coughing, dysphagia etc.
- Rapid drug therapy.
- Decrease in risk of choking during oral administration.
- MDT has good mouth feeling property and hence it increases its palatability.

Disadvantages

- They are hygroscopic in a nature and must be kept it dry place.
- They require special packaging for safety and stabilization of product.
- Larger dosage drugs are complicated to formulate in MDT.
- Patient suffering with sjogren's syndrome or dryness of mouth may not accept MDT due to decrease in saliva production.

CONVENTIONAL TECHNIQUES FOR FORMULATION OF MDT[16] [17] [18] [19]

Disintegrates Addition

It is a well reputed technique for formulation of MDT. The basic principle involves in formation of MDT by the addition of super disintegrants in ideal concentration so as it could easily dissolve in the mouth giving a good feel in the mouth.

Moulding

In this method, tablets are prepared by using hydrous ingredients so that tablets dissolve entirely and swiftly. The hydroalcoholic solvent is used to moisten the blend and moulded under pressure minor than that used in conventional tablet compression. Moulded tablets are slightly compacted than compressed tablets.

Sublimation

More hydrous ingredients are present in compressed tablets may even cause slow dissolution due to the low penetrability of tablets. So the unreactive solid ingredients are added which can be easily vaporized and increases the disintegration of tablets.

Freeze drying

It is the process where water is sublimated from the compound after freezing. Lyophilization is a technology that allows drying of thermo unstable drugs at low temperature which allows removal of water by sublimation. It further results in high porous preparation with a specific high area which disintegrated rapidly and increase absorption and bioavailability.

Spray drying

This method produces high perforated and fine powders that dissolve rapidly. The formulation may include non-hydrolyzed and hydrolyzed gelatins as supporting agents, mannitol as bulking agents, sodium starch glycollate as a super disintegrating agent, acidic material (citric acid), or alkaline material (baking soda) to enhance disintegration. The tablets disintegrate within 20 seconds in a hydrophilic medium when the spray drying method is used.

Wet granulation method

Wet granulation forms the granules, and the powders together by the process of binding resulting in adhesion.

A powder mixture is added into a slurry containing a binder, suspension, or solution Antiarrhythmic agents amiodarone disopyramide flecainide acetate quinidine. The method of introducing the binder relies on its solubility. It also depends on the components of its mixture especially the liquid plays an vital role in the granulation process. After completion of the process, the wet mass is milled and dried to form the granules. Then the wet mass is passed from a low-shear mill and dried for 8-24 hrs. After 24 hrs the granules which are formed are unified with excipients before compressing it into the tablet.

Dry Granulation
It is a process used in the formulation of granules by using an anhydrous solution because the product can be sensitive to heat, moisture, or both. There are two techniques to produce dry granules.[16]

Compression Granulation
It is used as a valuable technique where the operative dose of a drug is substantial for direct compression and the drug sensitivity increases when they come in contact with moisture, heat, or both, which excludes wet granulation. It involves 2 steps:

(1) Slugging
Slugs are compacted masses that are formed when the primary blend of powders is enforced into the dies of a massive capacity tablet press and the process is referred to as "slugging". The slugs are further milled or screened to produce granules.

(2) Roller Compaction
The screw conveyor system feeds the powder material between the rollers. Further, the compressed mass appears to be a thin wide ribbon that has fallen apart into large segments. Then these segments are milled or screened for the preparation of granules which are then unified with additional excipients before being compressed.

Mass extrusion:
An active blend becomes softer by incorporating the solvent mixture of hydrous PEG using menthol and expulsion of softened mass through syringe or extruder to get a sphere of outcome into even divisions using a heated blend for formation of tablets

Direct compression
It is a more convenient way to formulate tablets. It involves novel equipment commonly available excipient and negligible steps of processing. High dose can be accommodated and the final weight of the tablet can easily increase that of other production methods. The solubilization and disintegration of directly compressed tablets depend upon the individual or combined action of disintegrants, hydrous excipients, and effervescent agents. Example: Lamotrigine prepared by this technique using super disintegrants like Crosspovidone XL, Croscarmellose sodium, and Sodium starch glycolate.

Orasolv Technology
This technique has been introduced by 'CIMA' labs. In this process, the taste of active ingredient is masked. With help of the direct compression technique at minimal compression to reduce oral dissolution time, the tablets are formed. It requires only tablet machines and blenders. The final tablets are more friable and soft and they are packed in a specially designed pick and placed system.

Flash Dose Technology
'Fuisz' has patented this technology. Nurofen meltlet is the new type of ibuprofen that melts in the mouth. The Flash heating process forms shear from matrices which are known as floss.

Durasolv Technology
It is the patented technology by 'CIMA' labs. The tablets include drugs, lubricants, and fillers. Conventional tableting equipment is used to prepare these tablets hence it increases rigidity. A conventional packaging system is also used to pack the tablets like blisters. It is an apt technology for tablets requiring a low amount of active ingredients.

Zydis Technology
An active blend becomes softer by incorporating the solvent mixture of hydrous PEG using menthol and expulsion of softened mass through syringe or extruder to get a cylinder of outcome into even segments using a heated blend to form tablets**.** For coating granules of bitter taste drugs, the dried cylinder can also be used. Hence it marks in taste masking of acrimonious drugs.[9]

TECHNOLOGIES TO DEVELOP MDT

NONPATENTED

Freeze drying
Tablet molding
Spray drying
Mass extrusion
Sublimation
Cotton candy process
Direct compression
Melt granulation
Phase transition process

PATENTED

Zydus technology
Orasol technology
Durasolv technology
Wowtab technology
Dispersible tablet technology
Flahtab technology
Oroquick tehnology
Lyoc technology
Quick technology
Nanocrystal technology
Frosta technology
Pharmburst technology

MDT's In Market:

Due to its wide use (Table 1) and easy palatability, MDT is widely manufactured in the market. Various types of MDT's are existing in the market, some of them are listed below (Table 2).

This shows the wide interest of the manufacturers in this novel drug therapy.

Table1. Explored drugs(API) with their use for MDT[67]

Sr. No.	CATEGORY	DRUGS
1.	NSAIDS	Ketoprofen
		Piroxicam
		Paracetamol
		Rofecoxib
		Nimesulide
		Ibuprofen
		Tepoxaline
2.	Antiulcer	Famotidine
		Lansoprazole
3.	Antidepressants	Fluoxetine
		Mitraxepine
4.	Antiparkinsonism	Selegiline
5.	Antimigrane	Sumatriptan
		Rizatriptan
		Benzoate
		Zolmitriptan
6.	Anti-histaminic	Loratadine
		Diphenhydramine
		Buclizine
7.	Hypnotics and sedatives	Zolpidem
		Clonazepam
8.	Anti-psychotics	Olanzapine
		Risperidone

		Pirenzepine
9.	Anti-bacterial agents	Albendazole
		Bephenium
		Hydroxynaphthoate
		Pyrantel
		Embonate
		Thiabendazole
10.	Anti-arrhythmic agents	Amiodarone
		Disopyramide
		FlecainideAcetate
		Quinidine
11.	Anti-Epileptics	Beclamide
		Carbamazepine
		Clonazepam
		Ethotoin
		Methoin
		Methsuximide
		Phensuximide
		Primidone
		Sulthiame
		Valproic acid
12.	Anti-Hypertensive agents	Carvedilol
		Amlodipine
		Prazosin
		Terazosin
		Benidipine
		Darodipine
13.	Antineoplastic agent & Immunosuppressants	Aminoglutethimide
		Amsacrine
		Azathioprine
		Busulphan
		Mitoxantrone
		Procarbazine
		Tamoxifen citrate
		Testolactone
14.	Anti-fungal agents	Amphotericin
		Butoconazole Nitrate
		Econazole
15.	Cardiac Inotropic agents	Amrinone
		Digitoxin
		Digoxin
		Enoximone
		Lanatoside C
		Medigoxin
16.	Diuretics	Acetazolamide

		Triamterene
		Amiloride
17.	Anti-gout agents	Allopurinol
		Probenecid
		Sulphinpyrazone
18.	Anti-muscuranic agents	Atropine
		Benzhexol
19.	Nitrates and other anti-anginal agents	Amyl Nitrate
		GlycerylTrinitrate
		isosorbide dinitrate
		IsosorbideMononitrate
		PentaerythritolTetranitrate
20.	Anti-malarials	Amodiaquine
		Chloroquine
		Chlorproguanil
21.	Anti-coagulants	Dicoumarol
		Dipyridamole
		Coumalone
22.	Miscellaneous	Propyphenazone
		Spironolactone
		Phloroglucinol
		Sildenafil

Table 2. Market formulations of MDT [67]

Brand name	**Active ingredient**	Manufacturer
Alavert	Loratadine	Wyeth Consumer Healthcare
Rpimelt and Zooming ZMT	Zolmitriptan	Astra Zeneca
Hyoscyamine sulfate ODT	Hyoscyamine sulfate	ETHEX corporate
Cibalginadue FAST	Ibuprofen	Novartis consumer Healthcare
Nurofen Flash Tab	Ibuprofen	Boots Healthcare
Kemstro	Baclofen	Schwarz pharma
Fluoxetine ODT	Fluoxetine	Bioavail
Benadryl Fastmelt	Diphenhydramine	Pfizer
Zolpidem ODT	Zolpidemtartarate	Bioavail
Nasea ODT	Ramosetoron	Yarmanouchi
Ralivia Flash Dose	Tramadol HCl	Bioavail
Gaster D.	Famotidine	Yarmanouchi
Excedrin Quick Tabs	Acetaminophen	Bristol-myerssquibb
Claritin Red Tab	Loratadine	Sching corporation
Remeron Sol Tab	Mirtazepine	Organon Inc.
Feldene melt	Piroxicam	Pfizer
Maxalt-MDT	Rizatriptan benzoate	Merck
PropulsidQuicksolv	Cisapride monohydrate	Janssen
Pepcid ODT	Famotidine	Merck

Imodium Instant melts	LoperamideHcl	Janssen
Zyprexa	Olanzepine	Eli Lilly
Childrens Dimetapp ND	Loratadine	Wyeth consumer Healthcare
Zofran ODT	Ondansetron	Glaxo smith kline
Klonodin wafers	Clonaxepam	Roche
Risperidal M-Tab	Risperidone	Janssen
Zelapar	Selegiline	Elan American corporation
Zubrin (pet drug)	Tepoxaline	Schering corporation
Aricept ODT	DonepzilHcl	Eisai and Pfizer
Fazal co	Clonzapine	Alamo pharmaceuticals
Permax	Pergolide	Amarin corporation
Febrectol	Paracetamol	Prographarma
Domray MD	Domperidone	Ray Remedies
Mosid MT	Mosapride	Torrent
Nisure-MD	Nimesulide	Suzenpharma
Nimez MD	Nimesulide	Zotapharma
Valus	Valdecoxib	Glenmark
Zyrofmeltab	Rofecoxib	Zyduscadila
Torrox MT	Rofecoxib	Torrent
Romlast	Montelukast	Ranbaxy
OlanexInstab	Olanzepine	Ranbaxy
Zotacet MD	Cetirizine Hcl	Zotapharma
Benadryl Fast melt	Diphenhydramine and Pseudoephedrine	Lambert

SUPERDISINTEGRANTS

Superdisintegrants are additives that are present in ODT's for quicker and faster dissolution.

Superdisintegrants shows rapid disintegrating actions in tablets. By incorporation of superdisintegrants, the tablet dissolves within 5-300 seconds range with 100% bioavailability.

IDEAL PROPERTIES [10] [11][12] [13]

Good Flow and Compressibility Properties

Good flow powders are those powders that have 12-16% compressibility. e.g. crospovidone.

Poor Solubility

Both the mechanism and the rate of tablet disperssion can affect the solubility of the tablet. Water-soluble substances do not get disintegrated they get dissolved while a water-insoluble substance produces rapid disintegration. Hence for rapid disintegration, disintegrants must be less water-soluble.

Poor Gel Formation Capacity

Before the gels get released into the body, the drug is first diffused through the gel layer.

In tablet formulation, sodium starch glycolate is preferred as a super disintegrant at a conc: 4-6% w/w

Good Hydration Capacity

Hydrophobic drugs could adhere to disintegrant surfaces and influence the efficiency of these disintegrants and the comprehensiveness of their hydration. To minimize this problem, fast disintegrants of hydration capacity are added and hence enhance the dissolution.

METHODS OF INCLUSION [14] [15]

1. **Internal Addition (Intragranular) -** Before moistening, the powder is mixed with the granulating agent, the disintegrant is unified with additional powders. Hence the granules are combined by the disintegrant.

2. **External Addition (Extragranular) -** Before compression, the disintegrant is included in the sized granulation, and simultaneously mixing is carried on.

3. **Partly Internal and External-** The addition of disintegrants can be carried on in two steps internally or externally which immediately disrupts the tablet into earlier compressed granules while the disintegrating agent within the granules produces extra attrition of the granules to

the primary powder particulates. The 2 step method is preferred over the addition of the disintegrant on the granulating surface.

MECHANISM OF ACTION OF DISINTEGRANTS[14][21][43][60][61]

- Swelling
- Porosity and capillary action (Wicking)
- Heat of wetting
- Chemical reaction (Acid-Base reaction)
- Particle repulsive forces
- Deformation recovery
- Enzymatic reaction

Swelling

It is the most acknowledged mechanism for tablet disintegration as water penetration is the premitive step for tablet disintegration. When particles of disintegrants come in contact with water (medium) these particles swell and generate a swelling force due to which disintegration occurs.

When tablets have high porosity they show less disintegration due to improper swelling force and when the tablet has less porosity sufficient swelling force is developed. Also if the filling part is very huge, the liquid is unable to enter the tablet and disintegration again decelerates.

Capillary action and Porosity (Wicking):

Disintegrants that are unable to swell disintegrates by capillary action and penetrability. The pore present in tablets allows penetration of fluids in tablets. When the tablet is placed in the hydrous medium it enters the tablet replacing the absorbed air above the particles, which deteriorates the intermolecular bonds and disintegrates the tablet into small particles.

The water-absorbing capacity of the tablet is based upon tableting conditions and on the hydrophilicity of the drug/excipient.

Maintenance of minimal interfacial tension and porous structure towards hydrous fluid is essential which helps in disperssion which forms a linking around the drug particles which is hydrophilic. The fine-porous structure is important where wicking becomes a crucial factor and the permeability rate depends between opposite viscous forces and capillary.[57]

Capillary flow is described by Washburn's equation:

$L^2 = \left(\frac{\gamma cos\theta}{2\eta}\right) rt$

L is liquid penetration length into the capillary

γ is the surface tension,

θ is the solid-liquid contact angle

r is the pore size,

t is the time

η is the liquid viscosity

$L^2 = \left(\frac{\gamma cos\theta}{2\eta k^2}\right)$

K is Tortuosity factor

The value of k = unity for parallel capillaries.

The value of k may be up to 2.5, for a network comprising tortuous capillaries of different hydrodynamic diameters.

Hence, the equation shows

larger pore sizes will utilize more liquid uptake, which results in rapid disintegration.[58][59]

Heat of wetting

The disintegration of a tablet can occur due to the exothermic properties of these disintegrants. When these disintegrants get wet, they create localized stress due to capillary air expansion, which is the main reason for disintegration.

Chemical reaction (Acid-Base reaction)

When tartaric and citric acids react with alkali metal carbonates or bicarbonates (bases) in presence of water they liberate CO, this CO promotes the disintegration of the tablet since it generates pressure within the tablet. CO gas helps to dissolve the API into the water and also enhances the taste of the tablet. They are highly reactive to small changes in moisture and temperature hence environment regulation is strictly required for the preparation of the tablets.

Particle Repulsive Forces

According to Guyot-Hermann's particle repulsion theory, water enters tablets by using aqueous pores which creates a continuous starch network that carries water from one particle to another, which imparts substantial hydrostatic pressure. Then the water enters between starch grains due to its attraction towards starch surfaces. Which results in the breaking of hydrogen bonding and other forces. This creates an electric repulsive force between particles and promotes disintegration in presence of water.

Deformation Recovery

During compression, the shape of disintegrant particles is inaccurate which can be corrected by wetting in the pre-compression stage. This increases the deformation of particles which favors the breakdown of the tablet. Such a phenomenon is important for disintegrants such as starch and Crospovidone that show negligible swelling.

Enzymatic Reaction
Enzymes present in the body also show disintegrating action. These enzymes have the binding mechanism of binder and help in disintegration. Swelling causes a burst of tablets or increases the absorption of water. This leads to an extensive increase in the volume of granules to promote disintegration eg Enzyme: Amylase protease cellulose invertase and binder starch gelatin cellulose and its derivatives sucrose

TYPES OF SUPER DISINTEGRANTS
NATURAL:
Today many researchers had found the need for materials from plant origin as the pharmaceutical disintegrants. Due to bio-acceptable, renewable sources, local accessibility, ecofriendly nature, and cheap compared to vital synthetic products, plant products serve as a substitute to synthetic products. Polysaccharide hydrocolloids containing glucans, gums, and mucilages which are present in higher plants are copious in the environment.

MUCILAGE:
Mucilage is a glutin-rich substance while gums are concentrated mucilage. The main variation between mucilage and gum is that the gums are water-soluble and mucilages are water-insoluble. In (Table 3) information of majorly used mucilage as disintegrants are provided. Mucilage gives the ability to plants to hydrate themselves and to resist drought. Mucilage is a glutinous substance that mainly contains polysaccharides, proteins, and urbanites.

Table 3. SOME NATURAL MUCIALGE USED AS DISINTEGRANTS [31][32][33][34][35][36][37][38][39][40][41][42]

MUCILAGE (DISINTEGRANTS)	PROPERTIES & CONTENTS	DRUG	METHOD USED	RESULT
1.LEPIDIUM SATIVUM (ASALIYO)	Used as disintegrants & herbal medicine. Seeds: higher proportion of mucilage, dimeric imidazole alkaloids lepidine B, C, D, E, and F, and two new monomeric imidazole alkaloids semilepidinoside A and B. Swelling index: 18 Angle of repose: 32 ^{0}C Bulk density: 0.58g/cc Tapped density: 0.69g/cc.	NIMESULIDE	DIRECT COMPRESION	Disintegration time: 17 sec. Mean dissolution time: 5.27 sec (At 10% w/w concentration)
2.PLANTAGO OVATA MUCILAGE	Has various characteristics like sustaining, disintegrating, and binding properties. Swelling index: 89±2.2%v/v	PROCHLORPERAZINE MALEATE	DIRECT COMPRESSION	Dispersion time: 8 sec. (At 8% w/w concentration)
3 HIBISCUS ROSA SINENSIS MUCILAGE POWDER.	The plant contains methyl-2-hydroxysterculate, methyl sterculate, cyclopropanoids, β-rosasterol and 2-hydroxysterculate malvate. leaves consist of carotene (7.34 mg/100 g of new material) protein, moisture, carbohydrate, fat, calcium, fibers, and phosphorus	ACECLOFENA	DIRECT COMPRESSION	Disintegration time: 20 sec (At 6% w/w concentration)

4.FENUGREEK SEED MUCILAGE	Has wide applications as a food, a food additive, and as a traditional medicine in every region. Angle of repose: 22.25 ^{0}C Bulk density: 0.64g/cc Compressibility index respectively: 15.20%	MELTFORMIN HYDROCHLORIDE	DIRECT COMPRESSION	Disintegration time: 15.6 sec (100% drug release within 18 min at 4% w/w concentration)
5.CUCURBITA MAXIMA PULP POWDER	It has comparative friability and hardness hence the naturally obtained *Cucurbita maxima* pulp powder acts great as disintegrant.	DICLOFENAC SODIUM	WET GRANULATION	Disintegration time: 7.23 sec (At 2.5% w/w concentration)
6.OCIMUM GRATISSIUM SEED POWDER AND MUCILAGE POWDER	It mainly consists of polysaccharides, proteins, and uranides.	MELTFORMIN HYDROCHLORIDE	DIRECT COMPRESSION	Disintegration time: 43 sec (Mucilage powder at 5% conc)
7.CHITOSAN	Widely available polysaccharide after cellulose.	CINNARIZINE	WET GRANULATION	Disintegration time: 45 sec (Seed powder at 5% conc) Disintegrating time: 60 sec (At 3% w/w concentration)

GUMS

Gums[43]

Due to their ability to inflate in water, gums are widely used as disintegrants. Good disintegration property can be achieved (2-10% w/w of tablet weight) and the gum must be cautiously titrated to analyze the tablet. Commonly used gums (disintegrants) are karaya, agar, guar gums, pectin, gellan, and tragacanth.

Guar Gums[21] [44]

Guar seed extract contains 5-7% protein, 10% moisture, ash, 80% of galactomannan (guaran), and minimum presence of heavy metals. Neutral, completely soluble, free-flowing polymer is appropriate for usage in food. It is insensitive to solubility of the tablet matrix, pH, or moisture contents.

It does not have pure white color sometimes it differentiates in color from tan to off-white and discoloration may occur in alkaline tablets. It is superior to some common disintegrants such as alginates, magnesium aluminum silicate, corn starch, and celluloses. Finer particle sizes have greater deforming capabilities thus enhancing its dissolution.

Gellan Gums[21] [45]

Pseudomonas elodea produces Gellan gum which is a biodegradable polymer consisting of a rectilinear tetrasaccharide repeat structure and a rectilinear anionic polysaccharide. It is utilized as a disintegrating agent in tablet. It consists of monosaccharides, β-D-glucose, α-L-rhamnose, and β-D-glucuronic acid in a molar ratio of 2:1:1 associated together to form a rectilinear primary structure.

Due to its rapid swellable characteristics, the dispersibility of the tablet occurs when it comes in presence of water and shows its less lipophilic nature. Disintegration time: 4 min (At 4% w/w concentration) and 23 min (90% drug dissolution).

Gum Karaya[43] [45]

Gum exudates are available from the parts of Sterculiaurens affiliated with the family Sterculiaceae. It is an anionic polysaccharide. It contains 13% D-galactose, 43%. D-galacturonic acid, and 15 percent L-rhamnose. Karaya engrosses water and inflates to 60-100 times its real volume. Due to its high viscosity, its use is limited as a binder and disintegrant in the development of novel dosage forms.

Agar:[45]

It is the dried gelatinous substance synthesized by *Gelidium amansii* (Gelidanceae).

It is also obtained from Pterocadia (Gelidaceae) and Gracilaria (Gracilariaceae). It is white or yellowish-gray to nearly odorless, colorless with a mucilaginous taste. It is accessible in the form of coarse powder, sheet flakes, or strips.

It contains polysaccharides as agaropectin and agarose. Agarose (gel strength) Agaropectin (viscosity) of agar solutions.Due to its high gel strength, it also acts as a disintegrant. Gums are used in a conc from 1 to 10%. Due to their relatively low capacity development, they are not good as other disintegrants.

Starch[46]

It is the most accepted and traditional disintegrant in the medicinal industries. It penetrates the tablet matrix that allows water to enter the structure by capillary action. Hence it leads to disruption of the tablet. Regular corn starch USP has certain limitations. So it is substituted by evolved starches with special attributes and has specific properties.

starches and their different compounds have a variety of swellable attributes which may be accountable for the various dissolution and disintegration times.

Pregelatinized Starch (Starch 1500)[47] [48]

It is a form of starch prepared from potato starch and it has an ability to swell which promotes the disintegration of orodispersible tablets. It is a direct compactable form of starch that consists of intact and incompletely hydrolyzed cracked starch grains. It has many applications in formulations such as a disintegrant, binder, and filler. Active concentration is between 5-10%. Pregelatinized starch shows the swelling action.

Celluloses[20][48]

Depending on their agility to inflate on interaction with water, cellulose such as carboxymethylcellulose, methylcellulose, and purified cellulose are used as disintegrating agents.

Microcrystalline Cellulose

It is pure and incompletely depolymerized cellulose. It occurs as an odorless, tasteless, white, crystalline powder composed of porous particles. At a conc between 10-20% it servers a very good disintegrating property. It allows entry of water into the tablet matrix having capillary pores, which degrades the H-bonding between alternative bales of cellulose microcrystals. This starch is mainly used for rapid and effective disintegration in tablet formulation due to its rapid-wicking rate for water. A mixture of L-HPC and MCC in the range 2:8-1:9 shows the shortest disintegration time. Microcrystalline cellulose is available in various moisture grades and particle sizes that have different properties and applications as Avicel pH – 101(powder), pH-102(granules), pH-112(moisture sensitive).

Alginates[21]

They are colloidal and hydrophilic substances that are obtained from specific species of Kelp. In chemical forms, they are available as the sodium salt of alginic acid or alginic acid. Alginic acid is derived from seaweeds that contain D-mannuronic and L-glucuronic units. Due to its affinity for water absorption and high absorption capacity make it acts as an excellent disintegrant eg. alginic acid (1-5 %) concentration (shows best disintegrant property), Sodium alginate: 2.5-10 % concentration. It is preferably used with multivitamins formulation and ascorbic acid.

Chitin[49] [50]

Chitin is available in marine resources. They are present shells of crustaceans and insects. It contains acylated polyamine, which is non-toxic and biodegradable. After cellulose, they are the most abundant natural polymer. Tablets containing Chitin show better dissolution and faster disintegration. Its acts by water uptake from moisture in the atmosphere. Shell wastes of squid, shrimp, krill, lobster, and crab are important sources of chitin.

SYNTHETIC DISINTEGRANTS[24][25][26][27][28][29][30]

Low Substituted Hydroxy Methyl Cellulose

Due to its large particle size, it is used to prevent capping. Nowadays it is widely used in the wet granulation method and directly compressible method. The combination of low hydroxyl propyl cellulose and microcrystalline cellulose is used for rapidly disintegrating the tablet. With a ratio of 2:8 and 1:9 to get fast disintegration.

Micro Crystalline Cellulose
It has a porous structure and when water enters the hydrogen bonding between the cellulose particles. They are ruptured and it achieves good disintegration. It is partially depolymerized synthesized from alpha-cellulose. It is mainly used for the direct compression method. After compression, the MCC particles are deformed plasticity due to their slip planes and dislocation. Avicel 102 is used as diluents and also disintegrant because of its mechanism of interlocking due to its small size it also has advantages like rapid disintegration and more binding strength.

Calcium Silicate
It is light in weight. It disintegrates with an action of wicking when it is used in the concentration of 5%.

Chitin and Chitosan
The main mechanism of action for super disintegration is moisture absorption with water uptake while swelling also plays a small role in the dissolution of the tablet.

Starch partially pre-gelatinized
It is synthesized from starch grains in a directly compressed method with intact and partially hydrolyzed properties. It also helps by providing pharmaceutical aid like binder, filter, and disintegrant. The concentration mainly used is nearly about 5-10%. Swelling is the main mechanism of action.
It improved the tablet physical properties with a few steps leading to complex formation
and dramatically lower costs and help in rapid drug release.

Commonly used synthetic disintegrants with their pros and cons are mentioned in table 4.

Table 4. Commonly used synthetic superdisintegrants [18][19][20][21][22][23]

SYNTHETIC DISINTEGRANTS	PROPERTIES	EFFECTIVE CONCENTRATION	ADVANTAGES	DISADVANTAGES
CROSSPOVIDONE	SOLUBILITY: Water-insoluble Rapidly disperse and swell in water Higher rate of swelling Greater surface area SWELLING INDEX: 58±1.5%	RANGE: 1-3% w/w	Swells rapidly in water without forming a gel. It is highly compressible. Not affected by pH media.	There are no disadvantages because till now it has shown no side effects.
CROSSCARMELLOSE SODIUM	SOLUBILITY: Water-insoluble Instantaneously swells to 4-8 times its original volume in contact with water SPECIFIC SURFACE AREA: 0.81-0.83 m^2/g SWELLING INDEX: 65±1.7% v/v.	TABLET DISINTEGRANT: up to 5% w/w . DIRECT COMPRESSION METHOD: 2 % w/w	Uses a combination of wicking and swelling mechanism for disintegration. Disintegrates in 2 minutes, readily available, and low cost.	Has lower cross-linking density and form gels when fully hydrated. It is poorly compressible. It is anionic and may form complexes with cationic drugs.
SODIUM STARCH GLYCOLATE	Rapidly absorbs water Increase swelling up to 6%. SWELLING INDEX: 52±1.2% v/v.	WET-GRANULATION METHOD: 3 % w/w RANGE: 4-6% Above 8%, disintegration may increase due to its gelling and viscosity-producing effects.	Absorbs water rapidly and swells in water to the extent of 200-300%. Disintegrates within 2 minutes. Easily available and cheaper.	At a huge amount (>8%), disintegration increases due to gelling and succeeding viscosity-producing effects. Low cross-linking density. Form gels when fully hydrated. Poorly compressible. It is anionic and binds with cationic drugs.

CO-PROCESSED [51][52][53][54][55][56]

As individually all of the disintegrants have some of the disadvantages, to avoid this problem many disintegrants are used in combination. It not only increases the efficiency of the disintegrants but also has different characters like better flow, low/no moisture sensitivity, superior compressibility, and rapid disintegration ability which plays a significant role in the increased bioavailability and stability of the tablet. To acquire the need of tablet manufacturing, new and improved super disintegrants are developing. To get formulations with anticipated end effects the addition of various excipients is needed.

The interactions of two or more excipients at the sub-particle level to provide a synergy of functionality improvement and overcoming the undesirable properties of individual disintegrants are called co-processed disintegrants. It is utilized in the formulation of excipient granules with supreme properties compared with individual components or physical mixtures of components.[63]

Most commonly used co-processed disintegrants with their properties and components are mentioned in table 5.

TABLE 5. MOST COMMONLY USED CO-PROCESSED EXCIPIENTS DRUGS

Sr. No.	Name	Description	Application	Method used	Disintegration Time	Compositions
1.	LUDIFLASH	TASTE: Mild sweet taste and cooling effect in the mouth. FLOWABILITY: Superior flowability and low hygroscopicity. DISSOLUTION: Dissolves partially in organic solvents and water.	Excellent excipient for the direct compression method	Direct compression	27 sec	Mannitol, XL-PVP, PVAPEG Copolymer
2.	F-MELT	FLOWABILITY: Flows rapidly with circular dense particles. Cost-effective and Time-saving, capping or less sticking.	For direct compaction manufacturing of rapidly disintegrating oral tablets containing lubricants and APIs.	Direct compression using 10 % to 65% w/w	Less than 30 sec.	D-Mannitol, Xylitol MCC, Crospovidone, Fujicalin.
3.	PHARMABURST	It is an easy-to-use quick-dissolving delivery platform. It is smooth and creamy and is highly compatible.	It is flexible to innovate robust "Quick Dissolve" formulations, at a sensible cost.	Spray drying method	30 sec	Mannitol, Sorbitol
4.	POLACRILIN POTASSIUM	Do not form lumps after disintegration.	It is used as a both taste-masking agent as well a disintegrating agent.	Direct Compression	45 sec	Microcrystalline Cellulose (Avicel-102), Mannitol, Sodium Starch Glycolate, Crosspovidone, and Croscarmellose Sodium

Table 6 Examples of disintegrants and method used for their formulation

DISINTEGRANTS	METHOD USED
1] Doxylamine Succinate Croscarmallose sodium, Crospovidone, sodium starch glycolate(super disintegrants), Indion 234 (taste masking agent)	Batch method
2] Pheniramine Maleate Croscarmallose sodium, crospovidone, sodium starch glycolate, Ibuprofen Crospovidone (super disintegrant), Mannitol (sweetener), Atenolol Kyron T-314 (super fast disintegrants), Losartan potassium, Croscarmallose sodium, Polyplasdone XL-10, Explotab (super disintegrants), Chlorpromazine HCL Sodium starch glycolate, crospovidone, Croscarmallose sodium, LHPC, pregelatinized starch (super disintegrants), Oxcarbazepine Crospovidone (super disintegrant), aspartame (sweetener), PVP K-30 and Peg-6000 (solubility enhancers) Promethazine HCL, Eudragit E-100 (taste masking agent), crospovidone, sodium starch glycolate, Croscarmallose sodium (super disintegrants), Terbutaline sulfate Sodium CMC, Ac-Di-Sol , Levocetrizine HCL Sodium starch glycolate, Croscarmallose sodium, Baclofen Ac-Di-Sol, Sodium starch glycolate, crospovidone, Glipizide Crospovidone, Croscarmellose sodium, Lornoxicam Sodium starch glycolate, crospovidone, Croscarmallose sodium(super disintegrant) Beta cyclodextrin (taste masking agent), Combination of Omeprazole and Domperidone Kollidone CL, Ac-Di-Sol, sodium starch glycolate (super disintegrants),Mannitol (sweetening agent), Amlodipine besylate Crospovidone (super disintegrant), Mannitol, Aspartame, Acesulfame potassium (taste-masking agents and sweeteners), Metoprolol tartrate Plantago ovate mucilage (natural super disintegrant), Granisteron Hydrochloride Croscarmallose sodium, Indion 204,	Direct compression
3] Oxcarbazepine Crospovidone (superdisintegrant), aspartame (sweetener), PVP K-30 and Peg-6000 (solubility enhancers)	Solid compression
4] Acetaminophen Saccharides, Crystallized paracetamol PEG-6 stearate (waxy binder), Croscarmallose sodium (super disintegrant), Aceclofenac Sodium starch glycolate, Cross carmellose sodium, pregelatinized starch	Wet granulation
5] Crystallized paracetamol, PEG-6 stearate (waxy binder), Croscarmallose sodium (super disintegrant)	Melt granulation
6] Promethazine HCL Eudragit E-100 (taste masking agent), crospovidone, sodium starch glycolate, Croscarmallose sodium (super disintegrants)	Extrusion method
7] Levocetrizine HCL, Sodium starch glycolate, Croscarmallose sodium	Effervescent technique.
8] Aceclofenac Crospovidone, sodium starch glycolate (super disintegrants), Camphor(subliming agent), Amlodipine besylate Sodium starch glycolate	Sublimation.

COMMONLY USED DISINTEGRANTS [66]

LUDIFLASH:

Contents: It is a unique blend of mixtures containing polyvinyl acetate (5%), crospovidone (5%), and mannitol (95%).

Designed For: Direct compaction on high-speed tablet machine for a firm tablet with minimum friability.[53]

Manufactured by: BASF

Formulations:

1] Risperidone: Properties observed with the combination of ludiflash (co-processed disintegrant). Hardness of 56 N (10 mm round, flat tablets) and an extraordinarily low friability of less than 0.1 % at a compaction force of 4 kN.

2] Loperamide: Properties observed with the combination of ludiflash.

Hardness of 30 N (7 mm round tablets) at a compaction force of only 3.7 kN and minimum friability of less than 0.1 %.

Disintegration time: 11 sec leading to a dissolution rate of 95 % of the bio-active ingredient within 30 minutes.[64]

FMELT:

It is an excipient generally used in ODT containing saccharides, disintegrating agents, and inorganic excipients. It exhibits excellent tableting properties and also facilitates rapid water penetration which helps for the fast disintegration of the tablets. [65] It is a directly compactable excipient.

It has a shelf life of 3 years from the date of manufacture.

Contents: It is the mixture of Xylitol MCC, D-Mannitol, Crospovidone, Fujicalin

Manufactured by: Fuji chemicals

Properties: Has good moulding property that is well balanced with disintegrability.

Particles are heavy, circular in shape, and have high liquidity.

Disintegrating time: Not more than 30 seconds.

Global market: Patent acquired in India, Japan, and China, and other overseas countries. [73]

OTHER CO-PROCESSED DISINTEGRANTS

Cellactose 80:

Contents: Lactose, powdered cellulose

Manufactured By: MEGGLE

Applications: Direct compression, Roller compaction, and/or capsule fill.

MicroceLac 100:

Contents: Lactose, Microcrystalline cellulose

Manufactured By: MEGGLE

Applications: Direct compression, Roller compaction, and/or capsule fill.

Avicel DG:

Contents: Microcrystalline cellulose, Dibasic calcium phosphate

Manufactured By: FMC Biopolymer

Applications: Direct compression, Roller compaction, and/or capsule fill.

Avicel HFE 102:

Contents: Microcrystalline cellulose, Mannitol.

Manufactured By: FMC Biopolymer

Applications: Direct compression, Roller compaction, and/or capsule fill.

PROSOLV SMCC:

Contents: Microcrystalline cellulose, SiO_2

Manufactured By: JRS PHARMA

Applications: Direct compression, Roller compaction, Capsule fill, and wet granulation.

PanExcea MHC300G:

Contents: Microcrystalline cellulose, Crospovidone, Hydroxypropyl methylcellulose.

Manufactured By: Mallinckrodt-Baker.

Applications: Direct compression, Roller compaction with disintegrant functionality.

Ludipress:

Contents: Lactose, XL-Polyvinylpyrrolidone, soluble povidone.

Manufactured by: BASF

Applications: Direct compression, Roller compaction with disintegrant functionality.

StarLac:

Contents: Lactose, Starch

Manufactured By: MEGGLE

Applications: Direct compression, Roller compaction with disintegrant functionality.

PROSOLV ODT:

Contents: Colloidal silicon dioxide, Microcrystalline cellulose, Mannitol, Fructose, XL-Polyvinylpyrrolidone.

Manufactured By: JRS pharma

Applications: ODT

RetaLac:

Contents: Lactose, Hydroxypropyl methylcellulose.

Manufactured By: MEGGLE Applications: Controlled Released tablet formulations.

CONCLUSION:

MDT is easily accepted by traveling patients, geriatric as well as pediatric because of its ease of administration. The drugs of different categories can be easily formulated in MDT. MDTs are enriched with factors like enhanced palatability, fast action, increased bioavailability, and good stability improving patient compliance drastically.

To date, various companies are constantly involved in improving and discovering new disintegrants to make the MDT more efficient.

Nowadays, there is rapid progress in novel pharmaceutical excipients including disintegrants one can expect novel technologies for MDT as well as for disintegrants, in the future.

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