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ORALLY FAST DISINTEGRATING FILMS – A NOVEL DRUG DELIVERY SYSTEM

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ABSTRACT

This review article present the oral disintegrating film as a novel approach. The orally disintegrating films are the novel drug delivery system in today's scenario. It is the most popular and patient friendly method of medicines administration. This system is eminent of among pediatrics and geriatrics. Due to this simplicity, ability to prevent pain, this route is widely used. In this system the drug is swallowed which enters into the systematic circulation and gives desired effect. High stability, easy transportation, pleasant taste, ease of administration are some of it's advantages. It's formulation consideration involves active pharmaceutical ingredient, film forming polymers, plasticizers, surfactants, sweetening agents, saliva stimulating agents, flavoring agents and coloring agents. The method of preparation of orally disintegrating films involves the solvent casting method, semisolid casting, hot melt extrusion, solid dispersion extrusion and rolling method. The formulation is analyzed through various evaluation parameters. The orally disintegrating films are evaluated by thickness, dryness test, tensile strength, percent elongation, tear resistance, folding endurance, Young's modulus, transparency, contact angle, in-vitro disintegration test, in-vitro dissolution studies, swelling property, content uniformity, percentage moisture loss, surface pH test, organoleptic test, permeation studies, stability study parameters. This review article also involves the packaging of orally disintegrating films. Thus, this review article emphasize on the novel approach of orally disintegrating films which helps in enhancing bioavailability, onset of action and thus produce a desired therapeutic effect.

KEYWORDS: Solvent casting, hot melt extrusion, solid dispersion extrusion and compliance.

OBJECTIVE

To formulate orally fast disintegrating films for quick onset of action.

To improve patient compliance.

INTRODUCTION

As discovery and improvement of recent chemical retailers is a complex, high-priced and time ingesting procedure, so latest trends are shifting closer to designing and growing progressive drug delivery structures for current capsules. In evaluation to other current, speedy dissolving dosage forms, which include liophylisates, the speedy films can produced with a manufacturing system that is aggressive with the producing prices of traditional capsules.in this drug transport gadget the drug is both dissolved or swallowed, which then enters into the systematic move to supply the desired effect. Oral disintegrating capsules and oral disintegrating movies are the everyday examples of orally disintegrating drug delivery systems. a regular oral disintegrating movie is commonly same to the size of a postage stamp. Orally rapid disintegrating films had been to begin with brought inside the marketplace as breath fresheners and personal care products including dental care strips and cleaning soap strips.

Pharmaceutical corporations and customers alike have embraced orally disintegrating movies (ODFs) as a practical and prevalent alternative to standard over the counter (OTC) medicinal drug forms which include beverages, pills, and drugs. The drug shipping machine being very eminent among pediatrics and geriatrics is orally disintegratingfilms. Because of their simplicity, capability to prevent pain, adaptability and most significantly affected person compliance, oral routes of drug administration are broadly standard, account for among 50-60 % of all dosage bureaucracy. The maximum famous and patient - friendly approach of medicine administration is through the oral direction. regarding oral direction of drug administration, many substitutes have continuously been supplied via the usage of latest novel technologies for pediatrics, geriatrics, bedridden, nauseous and non-compliance patients.The ODFs advanced is based at the generation of the transdermal patch. This novel drug delivery system also can be useful for meeting contemporary desires of the enterprise.[1,3]

The orally disintegrating films are thin, rapidly dissolving films with a region that measures 5 to 20 cm^2 in length. it's far an extremely skinny film organized the use of hydrophilic polymers, which rapidly disintegrate and dissolves on tongue or within the buccal cavity to

release the lively pharmaceutical agent without ingesting and chewing. This comfort offers each advertising advantage and expanded patient compliance. it is an opportunity platform designed for the medicine having excessive first bypass metabolism for attaining better bioavailability.[6,7]

ADVANTAGES

1. High stability
2. Smooth transportation
3. Ease of dealing with and management
4. Oral strip generation affords an alternate direction for drugs with first bypass metabolism.
5. Ease of administration of movies to the patients tormented by dysphagia, motion sickness and intellectual issues.
6. No water vital for administration.
7. First-rate taste
8. Huge surface place provides fast disintegration and dissolution within the oral cavity.

DISADVANTAGES

1. Capsules that are risky at buccal pH can't be administered.
2. Tablets with high dose can not be included into the films.
3. Drugs which irritate the mucosa cannot be administered with the aid of this course.
4. As it's miles fragile and ought to be covered from water, it calls for special packaging.
5. As it is also have high temperature sensitivity requires steeply-priced packaging.
6. There may be no manner to mix larger doses.
7. Dose accuracy is a tough technical trouble.

Unique Functions of Orally Rapid Disintegrating Films[9]

1) Film must be skinny and stylish.
2) To be had in numerous size and shapes.
3) Unobstructive and rapid release
4) It should adhere to the oral hollow space without difficulty.
5) Need to approaches speedy disintegration with out water.

PROPERTIES DISTINGUISHING MECHANISM OF ORALLY DISINTEGRATING FILMS

Table No 2: properties distinguishing mechanism of orally disintegrating films.

Properties	Flash Release	Mucoadhesive Melt – Away Wafers	Mucoadhesive Sustained Released Films
Area $(cm)^2$	2-8	2-7	2-4
Thickness	20-70	50- 500	50-250
Structure	Single layer	Single or multilayer	Multilayer system
Excipients	Soluble hydrophilic polymers	Soluble hydrophilic polymers	Low/nonsoluble polymers
Drug phase	Solid solution	Solid solution or suspended drug particle	Suspension and /or solid solution
Application	Tongue (upper palate)	Gingival or buccal region	Gingival (other region in the oral cavity)
Dissolution	60 s	In few minutes forming gel	Maximum 8-10h
Site of action	Systemic or local	Systemic or local	Systemic or local

FORMULATION CONSIDERATIONS

1. Active Pharmaceutical Ingredients
2. Polymers
3. Plasticizers
4. Surfectants
5. Saliva Stimulating Agent
6. Flavouring Agents
7. Colouring Agents

1. Active pharmaceutical Ingredient[11,12]

1) A typical formation of the film incorporates 1-25% w/w of the drug.
2) Kind of active pharmaceutical ingredients may be brought through speedy dissolving films.
3) Small dose molecules are the first-class candidates to be incorporated in oral fast dissolving films.
4) Multivitamins up to 10% w/w of dry film weight became absorb inside the films with dissolution time of less than 60 seconds.
5) It's miles always beneficial to have micronized active pharmaceutical components on the way to improve the feel of the film and also for better dissolution and uniformity within the oral rapid dissolving films.

6) Many active pharmaceutical substances, which are ability applicants for oral fast dissolving films technology, have bitter flavor.
7) This makes the formulation uneatable especially for pediatric preparations.
8) Therefore earlier than incorporating the active pharmaceutical components inside the oral fast dissolving films, the taste desires to be masked.
9) Numerous elegance of drugs may be formulated as mouth dissolving films along with antiulcer (e.g. omeprazole), antiasthamtics (salbutamol sulphate), antitussives, expectorants, antihistaminics, NSAID'S (e.g. paracetamol, meloxicam, valdecoxib).

2. PLOYMERS[15-20]

- A polymer is a substance or cloth such as very big molecules called macromolecules, composed of many repeating subunits.
- Polymers are the most crucial aspect of the orally speedy disintegrating films.
- An expansion of polymers are available for education of rapid dissolving oral films. The usage of film forming polymers in oral films has attracted enormous interest in clinical and nutraceutical applications. The choice of film forming polymers, is one of the most important and critical parameter for the a hit improvement of film formula. The polymers can be used by itself or in combination to provide preferred film houses.

- The polymers used in orally disintegrating films method must be

a) Trustworthy and non-irritant.
b) With out leachable impurities.
c) Must not retard disintegration time of film.
d) Ought to have correct wetting and unfold ability assets.
e) Ought to have enough peel, shear, and tensile power.
f) With ease to be had. cheaper, Tasteless.
g) Sufficient shelf life.
h) Have to not resource in inflicting secondary infections in oral mucosa.

NATURAL POLYMERS

1) CHITOSAN AND CHITIN

- A biopolymer with a lot of promise is practice inside the biomedical field is chitosan.
- Chitin B- (1-4)- N-acetyl-D-glucosamine) is a polysaccharide located certainly in the shells of crab and shrimp.

- In place of the liberated amino acid group in chitosan, it has an amino organization this is covalently bonded to an acetyl institution.
- Chitin, the structural element of crustacean exoskeletons and the cellular walls of fungus are used to make chitosan for commercial use.

2) GUAR GUM

- Guar gum is an aqueously soluble, naturally occurring polysaccharide gum made from Cyamopsistetragonoloba seeds, a member of the Leguminosae family.
- It's far made of (1/6) linkages connecting linear polymeric chains of (1/4) -b- D-mannopyransoyl devices as a -D- galactopyranosyl units.
- Which include biocompatibility and biodegradability, Guar gum is extra significant in the area of biomedical programs and in drug transport.
- Guar gum is beneficial as thickening agent, suspending agent, stabilizing agent, and emulsifier in pharmaceutical generation.

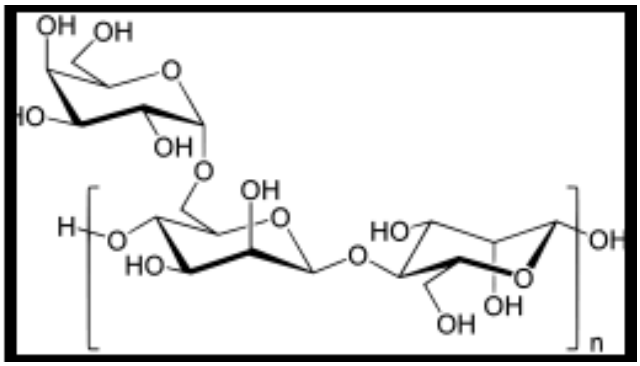

Fig. 1: Structure of Guar Gum.

3) GELATIN

- A complex mixture of highly molecular weighted water – soluble proteins makes up gelatin.
- Gelatin is obvious, brittle, in flakes or powder form, nearly flavourless, odourless, and barely yellow in color.
- In aqueous solutions among 30- 35°C, gelatin swells and absorbs 5-10 instances it's weight in water to form a gel.
- Gelatin is a herbal protein derived from collagen and is used notably in the food and pharmaceutical industries.
- Gelatin films produce a clean mouth feel, dissolve fast, make superb taste carriers.

- Gelatin movies have been determined to have an in – vivo dissolution time of 40 seconds and an in – vivo disintegration time of 8 seconds.

SYNTHETIC POLYMERS

❖ Artificial polymer is created artificially in lab via human being.

❖ A diffusion of chemical reactions on account that they do no longer exist in nature. It's far in addition categorised in main classes i.e.,

a) Biodegradable artificial polymers.

b) Non- biodegradable synthetic polymers.

1. The diverse film former used to form film like Polyvinyl alcohol, Polyvinyl pyrrolidone (PVP), Maltodextrin, Hydroxy Propyl Methyl Cellulose (HPMC), Hydroxy Propyl Cellulose (HPC), Methyl Cellulose (MC), Sodium Carboxy Methyl Cellulose (Na CMC) and so forth. are used as synthetic polymer.

NEGATIVE ASPECTS

- They value more money.
- They produce toxicity and aren't biodegradable in nature.
- The manufacturing method is hard.
- They're very marginally soluble in water.

1. HYDROXYPROPYL CELLULOSE

- Hydroxypropyl cellulose (HPC) is a thermoplastic non-ionic polymer this is water soluble.
- Poly (hydroxypropyl)ether of cellulose that has been in part changed with hydroxypropyl cellulose.
- It may include every other suitable anti-caking agent or NMT 0.6% silica. Commercially, HPC is offered in a many of grades with numerous solution viscosities .
- It's miles well known that movies made of polymers with extraordinarily excessive glass transition temperatures have a rigid consistency.
- The produced films were determined to be stiff, with a excessive elastic modulus and a totally low percent elongation (much less than 5%)and had been proven to display brittle fracture due to HPC’s relatively excessive glass transition term.

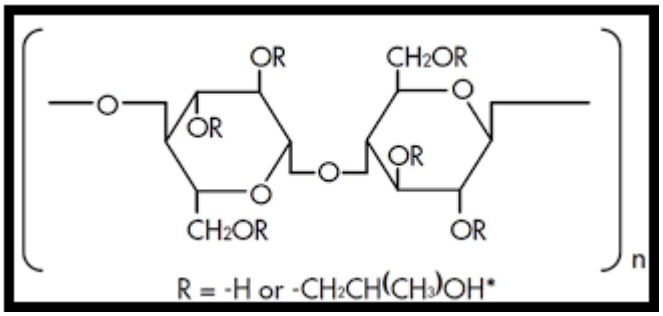

Fig. 2: Structure of Hydroxypropyl cellulose.

2. SODIUM CARBOXY METHYL CELLULOSE

a) Na CMC, or sodium carboxymethylcellulose, is crafted from alkali and mono-chloro-acetic acid treatment of cellulose the sodium salt, and so on.

b) Na CMC is cellulose ether non-ionic used regularly in hydrophilic matrix- managed launch systems.

c) It is able to accommodate, and it is non-toxic better medicinal drug loadings.

d) Na CMC is likewise an incredible film developer.

e) Products containing Na CMC or other hydrophilic polymers with vast potential are xanthan and HPMC medicine distribution to wet surfaces.

f) In an enzymatic manner modified CMC (carboxymethyl cellulose) is powerful at forming films belongings.

g) In step with reports, it's far used with different film forming polymers for oral movie guidance.

3. PLASTICIZERS[21,22]

- It's miles an primary ingredient of oral skinny films.
- The plasticizers assist to higher the mechanical properties of film such as tensile strength and elongation to the film.
- Version in their concentration may additionally have an effect on those houses.
- It also minimizes the brittleness of the film.
- It is able to higher the float and enhances the energy of polymer.
- The proper choice of the plasticizers is very foremost.
- It should be well matched with the drug, polymers as well as with the alternative excipients.
- The abnormal choice might also cause cracking, splitting and peeling of the film.

4. SURFACTANTS[23,24]

- Surfactants play a critical function as dispersing, wetting and solubilizing agent hence permitting films to disintegrate inside seconds freeing the incorporated drug, speedily.
- Usually hired are poloxamer 407, benzethonium chloride, sodium lauryl sulfate, tweens, benzalkonium chloride, and so forth.
- Out of these most predominantly used surfactants is poloxamer 407 this is used as solubilizing, wetting and dispersing agent.

5. SWEETENING AGENTS[25,26]

- Sucrose is the most usually used sweeteners in rapid dissolving oral films.
- Sucrose is very soluble in water and being colorless does not impart any undesirable color to the final formula.
- Neotame and Alitame are 2000-8000 instances sweeter than sucrose. Fructose has more sweetening power in comparison to sorbitol and mannitol.
- Sucralose was observed to be 600-1000 instances sweeter than sucrose while oral disintegrating films of donepezil had been evaluated for taste, after taste mouth feel.
- Aspartame and saccharin sodium are possibly to be 200and 300-500 instances sweeter compared to sucrose, respectively.
- It changed into additionally reported that sweeteners and flavors have minor effect on flexibility of film.

6. SALIVA STIMULATING AGENTS

- Salivary stimulants are normally acidic in nature stimulating the manufacturing of saliva in buccal cavity, consequently, selling the disintegrating of ODFs.
- Examples of saliva stimulating agents are citric acid, malic acid, tactic acid, ascorbic acid and tartaric acid.

7. FLAVORING AGENTS

- Flavors used within the method have to be non toxic, soluble, strong and like minted with the excipients.
- Flavors are needed to mask the bitter or nauseating taste of included drug.
- The quantity of flavoring agent required to mask the flavor depends at the taste kind and it’s strength.
- Any US-FDA approved taste can be used which includes sweet, sour or mint taste.

- One of the studies work established that mint, licorice and sucralose combination flavors accurately masks the bitter flavor of diclofenac sodium.
- Electronic tongues are used to discriminate the impact of diverse flavor protecting agents.

8. COLORING AGENTS

- A complete variety of colors is available, consisting of FD&C approved shades, eu colorings, natural shades and custom pantone – matched colors.
- Pigments are used as coloring dealers.
- Titanium dioxide is maximum broadly used colorant in ODFs and diverse different pharmaceutical preparations.
- The coloring agents must now not exceed concentration stages of 1% w/w.

Standard composition of orally disintegrating films

Table No. 2: Standard composition of orally disintegrating.

Ingredients	Amount	Examples
Plasticizers	0-20%w/w	Glycerol, dibutylpthallate, polyethylene glycol, etc
Saliva stimulating agents	2-6%w/w	Citric acid, malic acid, lactic acid, and ascorbic acid
Sweetening agents	3-6%w/w	Saccharin, cyclamate, and aspartame
Water soluble polymer	45% w/w	HPMC E3, E5 and E15 and K-3, Methyl cellulose A-3, A-6 and A-15, Pullulan, Sodium alginate, Hydroxypropylcellulose, pectin, gelatin, polyvinyl alcohol, etc
Active pharmaceutical ingredients	5-30% w/w	Antiallergic, antiemetic, antiepileptic, antimigrant
Surfactants	q.s.	Sodium lauryl sulfate, benzalkonium chloride, `tween, etc
Fillers, colors, flavors	q.s.	FD and C colors, US FDA approved flavors

CONVENTIONAL APPROACHES USED FOR THE FORMULATION OF ORALLY DISINTEGRATING FILMS

1. Solvent casting method
2. Semisolid casting
3. Hot melt extrusion
4. Solid dispersion extrusion
5. Rolling method

TECHNOLOGIES

1. SOLULEAVES™

Quite a number oral delivery movies that could comprise lively substances, colors and flavours are produced the usage of the era referred as SOLULEAVES™. The delivery device may be used for the cough or bloodless, gastrointestinal and ache therapeutic areas along side turning in dietary products. SOLULEAVES™ films may be designed to dissolve rapidly on touch with saliva, which purpose speedy launch of lively pharmaceutical substances and flavours. A large range of merchandise requiring speedy launch of drug within the mouth are administered the use of this delivery technique. This technique of management is especially beneficial for paediatric patients who can also have difficulty in swallowing drugs or tablets, conventional dosage paperwork. SOLULEAVES™ films can also be designed to stick to mucous membrane and to launch the active pharmaceutical factor slowly over 15 min.

2. FOAMBURST™

FOAMBURST™ is a special variant of the SOLULEAVES™ generation wherein an inert gasoline is passed into the film at some point of manufacturing. This outcomes in a film with a honeycombed structure, which dissolves hastily giving a novel mouth sensation. FOAMBURST™ has attracted hobby from food and confectionary manufacturers as a method of sporting and releasing flavours.

3. WAFERTAB™

WAFERTAB™ is a drug shipping gadget that includes lively pharmaceutical substances into an ingestible filmstrip. When the strip comes into contact with saliva in the mouth, this system presents fast dissolution and release of energetic pharmaceutical elements. A diffusion of styles and sizes are to be had for the instruction of WAFERTAB™. It's far a perfect technique for delivery of drug treatments, that are administered to the patients who've issue in swallowing and which calls for speedy release of the drug. The WAFERTAB™ filmstrip may be flavoured for additionally advanced flavor masking.

4. XGEL™

XGEL™ is on the heart of Meldexglobal's highbrow property, utilized in all its film systems and its ingestible dosage delivery technologies. XGEL™ films have the capability to comprise energetic pharmaceutical components. XGEL™ film can be flavor masked, coloured, layered and are succesful of having enteric residences. those film gives unique product benefits for pharmaceutical and healthcare merchandise. it is non-animal-derived,

authorised on non secular floor and is suitable for vegetarians. XGEL™ film is genetically modified organism (GMO) free film. Its continuous production offers an financial and competitive production platform. The XGEL™ film machine is soluble in either cold or hot water and may made to encapsulate any oral dosage form. The XGEL™ film includes a selection of different water-soluble polymers, particularly optimised for the intended use. All of the XGEL elements are well known and generally referred as safe (GRAS).

EVALUATION PARAMETERS

1. Thickness

The thickness of film is measured by means of micrometer screw gauge or calibrated digital Vernier Caliper. Suggest average is calculated eventually. Generally, three readings from all of the batches are determined and common is calculated. The width of film ought to be in range 5 – 2 hundred um. The thickness ought to be evaluated at 5 one-of-a-kind places (four corners and one at middle). Accuracy of dose distribution within the film is directly related to the uniformity within the thickness of Film.[31,32]

2. Dryness Test

This test is achieved to discover the capacity of a film to get adhered to a bit of paper pressed between strips. Tack is the tenacity with which the strip adheres to an accent that has been pressed into contact with films. In all there were eight levels recognized for film drying and these are set-to-touch, dust-free, tack-loose (surface dry), dry-to-contact, dry-tough, dry-through (dry-to-deal with), dry-to-recoat, and dry print-free. despite the fact that those exams are essentially used for paint films most of the studies can be change intricately to assess pharmaceutical ODFs. Dryness or tack check can also be performed with the help of a few newly invented instruments.

3. Tear Resistance

Tear resistance is the resistance which a film offers while some load or force is implemented at the film specimen. most force required to rip the film is measured as tear resistance value. Essentially very quick fee of loading 51mm (2 in)/min is hired and is designed to degree the force to being tearing. The unit of tear resistance is Newton or kilos -force. maximum force required to rip the specimen is known as tear resistance.[35]

4. Transparency

To decide transparency of oral film, a simple ultraviolet (UV) spectrophotometer may be used. Cut the film sample into rectangles and located on the inner facet of the spectrophotometer cellular. Transmittance of the film is labored out at 600nm wavelength. The transparency of the film is calculated via using system.

Transparency =(logT600)/b=-€c. Where T600 is the transmittance at 600 nm and b is the film 600 thickness (mm) and c is concentration.

5. Content Uniformity

Contents of a film are determined through popular assay method detailed for man or woman drug in special pharmacopoeia. Content uniformity is determined by way of estimating the API content material in character strip. This take a look at is done on 20 samples the usage of analytical techniques. According with Japanese pharmacopoeia the recognition value of the take a look at is less than 15%. Restrict of content material uniformity is 85-115% with the same old deviation of much less than or identical to 6%.

6. Organoleptic Test

The preferred organoleptic homes a quick dissolving method ought to have are coloration, flavor, and flavor. unique controlled human flavor panels are used for such cause. Taste sensors are utilized in In-vitro flavor assessment of ODFs for screening. because the components will collapse inside the oral cavity so it should provide acceptable organoleptic palatable traits. As oral films are more often than not administered to kids, shade makes a system acceptable among them. Therefore, coloration of formulation need to be uniform and attractive. The flavor used in the components ought to offer correct odor to the components. Taste is also an critical thing which must be evaluated. unique human taste panels are used to evaluate the flavor.[39,40]

7. Stability

Balance have a look at have to be finished in line with the international convention on Harmonization (ICH) tips. Balance checking out of the prepared formulation is mainly geared up to check whether or not it's far a stable product or no longer. The willpower of impact of temperature and humidity on the stability of the drug for the real storage is likewise completed the use of stability trying out. Firstly, it became wrapped in a butter paper then above it an aluminium foil was wrapped and the packing should be located in an aluminium pouch and make it heat sealed. System should be stored at 45°C, 75% RH for 3 months.

After, three months, the films have been evaluated for drug content material, disintegration time, and bodily appearance remark.

8. Packaging

A spread of packaging alternatives are available for fast- disintegrating films. Unmarried packaging is mandatory for films, which might be pharmaceutical merchandise. Packaging for oral skinny films consists of foil paper or plastic pouches, single pouch, aluminium pouch, blister packaging with more than one gadgets and barrier films. APR- Labtec has developed the speedy card, a proprietary and patented packaging machine, which is in particular designed for the rapid films. The speedy card is of equal size as a credit card and maintain 3 films on every aspect. Each dose can be taken out for my part. The films are synthetic by way of a laminating method and packaging fees are comparable to pills.

SUMMARY

- The orally rapid disintegrating films are skinny, unexpectedly dissolving films with a sector that measures 5 to 20 cm^2 in length. It's far an extremely skinny film organized using hydrophilic polymers, which rapidly disintegrate and dissolves on tongue or within the buccal hollow space to release the active pharmaceutical agent without consuming and chewing.
- The benefits of orally speedy disintegrating films entails smooth transportation, no water essential for application, it has quality flavor, large surface vicinity offers fast disintegration and dissolution within the oral cavity, high balance, ease of managing and administration, and so forth.
- The system attention of the orally fast disintegrating films includes Active pharmaceutical ingredients, Polymers, Plasticizers, Surfactants, Sweetening agents, Saliva stimulating agents, flavoring agents, coloring agents.
- The orally speedy disintegrating films can be organized by using the following techniques of coaching which involves solvent casting technique, semisolid casting, hot melt extrusion, solid dispersion extrusion, rolling method.
- The orally fast disintegrating films are evaluated via various parameters.
- The drug shipping system being very eminent amongst pediatrics and geriatrics is orally disintegrating film as compared to orally disintegrating pills. In comparison to other present fast dissolving dosage bureaucracy, which consist of liophylisates the speedy

films can produced with a manufacturing process that is competitive with the producing prices of conventional capsules.

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