Quick API delivery

The authors consider the advantages of using rapidly dissolving films to accurately and effectively deliver pharmaceutical ingredients, with an emphasis on the importance of controlling moisture content and drug loading during formulation development.

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Rapidly dissolving dosage forms (RDDFs) have become increasingly important because of their unique properties.[1,2] They quickly disintegrate and dissolve, and can be administered without water, making them particularly suitable for paediatric and geriatric patients. Tablets are the most commonly used type of RDDF. Orally disintegrating drug delivery systems were originally devised by scientists at Wyeth Laboratories in the UK during the 1970s and this research lead to the patenting of Zydis formulations. These patented formulations a are freeze dried type of dosage form, which possesses better convenience for use, enhanced bioavailability, and higher stability of the dosage form.

An ideal RDDF has the following properties:

- Good stability.
- Easily transported.
- Ease of handling (i.e., no special requirements for packaging and processing).
- Water is not required for administration.
- Pleasant taste.

RDDFs can be manufactured by a variety of technologies, including direct compression, wet granulation, freeze drying, spray drying and vacuum drying.

Orally disintegrating tablets

RDDFs are mostly available commercially in tablet form and are designed to dissolve/disintegrate in the patient's mouth within a few seconds, without the need to swallow or chew.[3,4] On administration, the tablet disintegrates in less than 1 min to form a suspension that can be easily ingested. Some patented orally disintegrating tablets (ODTs) technologies are summarized in Table 1.

Patented technology	Technology	Manufacturer
Oradisolv	Direct compression	Cima Labs Inc.
Durasolv	Direct compression	Cima Labs Inc.
Zydis	Lyophilization	R.P. Scherer Inc.
FlashTab	Multiparticulate compressed tablet	Ethypharm
Wowtab	Compressed moulded tablet	Yamanouchi Pharma Tech Inc.
Quicksolv	Lyophilization	Janssen Inc.
Lyoc	Lyophilization	Farmlyoc
Rapitab	Direct compression	Schwarz Pharma
Zydis	Moulding	Eurand Pharma
Flashdose	Cotton candy process	Fuisz Tech Ltd.

Table 1 Patented technologies for ODTs.

ODTs have high porosity, low density and low mechanical strength. Special packaging requirements are required for ODTs because of their high friability. This is more expensive

and it is sometimes challenging to transport and store these tablets. There is also a major concern regarding the ease of swallowing and even the possibility of choking when using an ODT, which makes it difficult to administrate them to paediatric and geriatric patients. This has led the pharmaceutical industry to develop alternative dosage forms that dissolve quickly in the patient's mouth and release the ingredients without the need of water.[5]

Rapidly dissolving films

Rapidly dissolving films (RDFs) have recently gained popularity in the form of breath fresheners.[2,5–7] These films are placed in the mouth and dissolve quickly to release the flavour. RDFs are already being used in breath-freshening products from Warner Lambert and Wrigley's in the US and Europe, and Boots in the UK, as well as in vitamin products. Zengen recently launched a chloraseptic relief strip in the US to deliver benzocaine — a local anaesthetic to treat sore throats. This delivery system is simply placed on a patient's tongue or any oral mucosal tissue. Instantly wet by saliva, the film rapidly hydrates and adheres onto the site of application. It then rapidly disintegrates and dissolves to release the medicament mucosal absorption or, with modifications, allows oral gastrointestinal absorption with a quick-dissolving aspect. The advantages of RDFs are:

- faster absorption[6.7]
- improved portability
- ease of administration
- accurate dosing
- cost-effectiveness
- improved patient compliance.

Suitable candidates for RDFs are nicotine replacement transdermal delivery (NRTD), and anti-ulcer and antihistamine drugs. Antipsychotic and sleeping disorder drugs are also potential candidates for prescription products.

Certain issues should be considered when developing RDFs:

- Drug loading is a major concern for RDFs. It can be increased by increasing film thickness. However, this can change the characteristics of the RDF to a slowly disintegrating film.
- Overcoming the unwanted taste of certain APIs can also be a challenge to the formulator.
- Dry storage conditions are also essential to maintain stability.
- Patients ingesting films of an API such as diphenylhydramine must be cautioned about the drowsiness effects it is likely to produce immediately because of the rapid action of these dosage forms.
- The patient may easily carry the medication at all the times so he/she should be warned against taking the films beyond normal recommended dosage schedules.[6]

Manufacturing RDFs

One (or a combination) of the following processes may be used to manufacture the RDF:[2]

- solvent casting
- semi-solid casting
- hot-melt extrusion
- solid dispersion extrusion
- rolling.

Solvent-casting method

The RDF is preferably formulated using the solvent-casting method, whereby the water-soluble ingredients are dissolved to form a clear viscous solution. The API and other agents are dissolved in smaller amounts of the solution, and combined with the bulk. This mixture is then added to the aqueous viscous solution. The entrapped air is removed by vacuum. The resulting solution is cast as a film and allowed to dry, which is then cut into pieces of the desired size. Water-soluble hydrocolloids used to prepare RDFs include:

- hydroxypropylmethyl cellulose (HPMC)
- hydroxypropyl cellulose (HPC)
- pullulan
- sodium alginate
- pectin
- carboxymethyl cellulose (CMC)
- polyvinyl alcohol (PVA).

Hotmelt extrusion

Hot melt extrusion (HME) is commonly used to prepare granules, sustained-release tablets, transdermal and transmucosal drug delivery systems.[8,9] Processing films by this technique, involves shaping a polymer into a film via the heating process rather than through the traditional solvent casting method.

Advantages of hot melt extrusion for film formation include:

- No need to use solvent or water.
- Fewer processing steps.
- Compressibility properties of the API may not be of importance.
- Good dispersion mechanism for poorly soluble drugs.
- More uniform dispersion of the fine particles because of intense mixing and agitation.
- Less energy compared with high shear methods.
- Improved bioavailability of the API.

Usually, when designing RDFs, polymers with low molecular weight or viscosity, such as HPMC E5 or pullulan PI–20, are preferred. A combination of various grades of polymers may also be used to achieve desired physical properties. Mixing polymers of high and low

viscosity produces a film with good mechanical strength and high drug solubility in the film.[10]

The HME process has recently gained popularity in the pharmaceutical industry. Building on knowledge from the plastics industry, formulators can extrude combinations of drugs, polymers and plasticizers into various final forms to achieve desired drug-release profiles.[8]

Repka *et al*. studied the influence of chlorpheniramine maleate (CPM) on topical HPC films by HME.[8] CPM has been reported to function as an effective plasticizer, increasing per cent elongation and decreasing tensile strength in concentration dependent manner. CPM also acted as a processing aid in the extrusion of hot melt films and allowing film processing at lower temperature.[11]

A study conducted by Repka *et al*. provided the overview of HME technology and investigated the *in vivo* bioadhesive properties of HPC films containing seven polymer additives on the epidermis of human subjects.[12] HPC films containing additives with and without plasticizer were prepared by HME. Incorporating carbomer 971P and a polycarbophil into HPC films increased bioadhesion significantly.

Therapeutic applications

RDFs have recently been introduced for a variety of therapeutic applications.

Procter and Gamble has patented an edible film with at least two essential oils (mint and spice) from Group A and at least one essential oil (citrus) from Group B.[13] This essential oil composition can effectively kill and remove oral microbials, which are related to the formation of biofilm in the oral cavity. Several grades of Methocel (Dow Chemical Company), xanthan gum, locust bean gum, carrageenan and pullulan were used as film-forming agents.

Chen *et al*. at Lavipharm Lab. Inc. have patented quick dissolving oral mucosal drug delivery devices having a mucosal surface-coat-forming inner layer disposed between two moisture barrier coating layers.[14] Drugs used in the study were nicotine and sildenafil. Pullulan and HPMC E3, E5, E15 and K3 were used as film-forming ingredients.

Riker Donald and his research team formulated RDFs for a weight-loss drug consisting of APIs and excipients that rapidly dissolve in the bucco-oral cavity.[15] The film may be absorbed, acting systemically or locally to provide the user with a sensory experience to reduce the appetite or prevent eating. Ginseng and gellan gum were used as a drug and a polymer respectively.

An RDF was formulated by Chen *et al*. containing nicotine and one or more non-microbial hydrocolloid(s). The film dissolves when applied intraorally to release the nicotine, which is absorbed through the oral mucosa reaching directly the systemic circulation.[16]

Fadden *et al*. prepared a consumable film adapted to adhere to and dissolve in the oral

cavity, comprising a modified starch, dextromethorphan and, optionally, at least one water-soluble polymer.[17]

A method of making a confectionery packet formed with an edible film and which encloses a centre composition is provided by Carroll *et al*.[18] The sachet is designed to be placed in the mouth, where the film dissolves and the centre composition is released. The centre composition consists of a sugar alcohol, such as xylitol, that creates a cooling sensation. Many flavours and colours may also be used in the centre compositions along with breath-freshening, antibacterial or pharmaceutical agents. The edible packet contains the film comprising HPMC, CMC and carrageenan.

A manufacturing method for oral quick-dissolving capsules is provided by Suzuki and co-workers, which consists of preparing a core liquid containing filler material;[19] preparation of a shell liquid that includes plasticizer and a shell-forming agent, and the formation of the seamless capsules with a diameter of 1–10 mm. Gelatine and glycerine were the main ingredients used in the manufacture of these quickly dissolving capsules.

Table 2 List of marketed films containing APIs.

A new technique is applied in manufacturing a capsule made from foamed film, whereby gas is blown into the film during production, thus giving it a honeycombed structure. The voids in the film may be gas filled, empty or filled with other materials to produce specific taste-burst characteristics or to deliver the API. The light honeycombed film structure results in capsules that dissolve rapidly, releasing the contents into the oral cavity.[20] Lavipharm Laboratories Inc. has recently invented an intraoral, fast-dissolving drug delivery system, Quick-Dis. It is a thin, flexible and quick-dissolving film, which is placed on the tongue. It is retained at the site of application and rapidly releases the active agent for local and/or systemic absorption.[21] A list of marketed films containing the API is shown in Table 2.

The following *in vitro* and *in vivo* tests are conducted to evaluate the qualities of a RDF:[2,21]

- Drug loading capacity.
- Mechanical testing, including thickness, tensile strength, percentage elongation, Young's Modulus, dry and wet tack, bending length.
- Surface morphology study using scanning electron microscopy (SEM).
- Disintegration and dissolution study using various dissolution media (i.e., distilled water, simulated saliva).
- *In vivo* animal and human safety studies. An animal safety study can be conducted using various models. A common example is the hamster cheek pouch model. In this study, the film is given to the animal twice a day for 4–5 consecutive days. The film is retained in the pouch for 10 min and then rinsed-off using distilled water. The pouch is observed for any adverse effects immediately and after a 24 h interval. The clinical irritation study on human beings can also be similarly conducted. The site of application and the oral mucosa should be evaluated for any irritation before and after the application immediately 1 h and 24 h of application.[2]

Conclusion

RDDFs are becoming important drug delivery systems because of their rapid disintegration and possibly improved dissolution characteristics. Most of the commercially existing RDDFs are in the form of ODTs. RDFs, a newer class of the RDDFs, have gained more popularity because of their portability, patient compliance, faster absorption and ease of administration. RDFs can be manufactured by solvent casting or hot melt extrusion techniques. They can be applied by oral and buccal routes and can be used in breath fresheners, local anaesthetics, vitamin supplements and in cold-allergy remedies. The evaluation of RDFs is done by various *in vitro* and *in vivo* methods. In the future, more pharmaceutical companies could be interested in RDFs for delivering a wide range of APIs.

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Key points

- RDFs provide a unique way for rapid delivery of the API.
- As compared to tablets, they provide distinct advantages such as ease-of-use, improved portability and faster absorption.
- These types of RDF may be conveniently used for a variety of therapeutic agents.
- Drug loading and storage criteria need to be given consideration during its formulation development.

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