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A REVIEW ON- RECENT ADVANCEMENT IN THE DEVELOPMENT OF RAPID DISINTEGRATING TABLET

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ABSTRACT

Recent advances in novel drug delivery (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for ease of administration and to achieve better patient compliance. In the recent trend one such approach the development of rapid disintegrating tablets formulation is emerging and gaining popularity because it is easy to administer and leads to better patient compliance. These dosage forms are placed in the mouth, allowed to disperse or dissolve in the saliva. They release the drug as soon as they come in contact with the saliva, thus obviating the need for water during administration. The aim of this article is to review the progress of the evolving technologies and super disintegrating agents in the formulation, manufacturing and evaluation of these tablets. This article also discusses the new evaluation methodologies for these rapid disintegrating tablets. Various modifications in the conventional evaluation and use of specialized instruments are found to be essential in the testing of these dosage forms. In the present review the formulation techniques and different technologies are discussed.

Keywords: Rapid disintegrating tablet, Mechanism, Conventional techniques, Patented technology.

1. INTRODUCTION

In recent decades, a variety of pharmaceutical research has been conducted to develop new dosage forms. Considering quality of life, most of these efforts have been focused on ease of medication. Among the various dosage forms developed to improve the ease of administration, the Rapid Disintegrating tablet (RDT) is the most widely preferred commercial products *(Nayak S et al)*. The oral cavity is an attractive site for the administration of drugs because of ease of administration. Various dosage forms like Tablets, Capsules, Liquid preparations are administered by oral route. During the last decade, Rapid Disintegrating tablet (RDT) technologies that make tablets disintegrate in the mouth without chewing and additional water intake have drawn a great deal of attention *(Sharma S)*.The RDT is also known as fast melting, fast dispersing, rapid dissolve, rapid melt, and or quick disintegrating tablet. All RDTs approved by the Food and Drug Administration (FDA) are classified as orally disintegrating

tablets. Recently, the European Pharmacopeia adopted the term orodispersible tablet for a tablet that disperses or disintegrates in less than 3 minutes in the mouth before swallowing. Such a tablet disintegrates into smaller granules or melts in the mouth from a hard solid to a gel-like structure, allowing easy swallowing by patients. The disintegration time for good RDTs varies from several seconds to about a minute *(Fu Yourong et al, Chaudhari PD et al)*. Rapid disintegrating tablets provide an advantage particularly for pediatric and geriatric populations who have difficulty in swallowing conventional tablets and capsules (Nayak UK et al). Additionally, pediatric patients may suffer from ingestion problems as a result of underdeveloped muscular and nervous control. Moreover, patients traveling with little or no access to water, limit utility of orally administered conventional tablets or capsules. Rapid Disintegrating tablet results in quick dissolution and rapid absorption which provide rapid onset of action. Moreover, drug candidates that undergo pre-gastric absorption when formulated as RDTs may show increased oral bioavailability. It provides good stability, accurate dosing, easy manufacturing *(Prajapati GB and Patel SB, Mohan A and Ghosh SK)*.

1.1. Ideal Properties

An ideal RDT should:

- Require no water for oral administration.
- Have a pleasing mouth feel.
- Have an acceptable taste masking property.
- Be harder and less friable.
- Leave minimal or no residue in mouth after administration.
- Exhibit low sensitivity to environmental conditions (temperature and humidity).
- Allow the manufacture of tablet using conventional processing and packaging equipments. *(Sharma S)*

1.2. Advantages

- Administration to the patients who can not swallow, such as the elderly, bedridden patients, patients affected by renal failure & patients who refuse to swallow such as pediatric, geriatric & psychiatric patients.
- Rapid drug therapy intervention.
- Achieve increased bioavailability/rapid absorption through pre-gastric absorption of drugs from mouth, pharynx & esophagus as saliva passes down.
- Convenient for administration and patient compliant for disabled, bedridden patients and for travelers and busy people, who do not always have access to water.
- Good mouth feel property helps to change the perception of medication as bitter pill particularly in pediatric patients.
- The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.
- New business opportunity like product differentiation. *(Kumari S et al)*

1.3. Salient Features

- Ease of administration to patients who refuse to swallow a tablet, such as pediatric and geriatric patients and, psychiatric patients.
- Convenience of administration and accurate dosing as compared to liquids.
- Rapid dissolution of drug and absorption which may produce rapid, onset of action.
- Some drugs are absorbed from the pharynx and esophagus as the saliva passes down into the stomach, in such cases bioavailability of drugs is increased.
- Ability to provide advantages of liquid medication in the form of solid preparation.
- Pre-gastric absorption can result in improved bioavailability and as a result of reduced dosage, improved clinical performance through a reduction of unwanted effects. *(Sharma S)*

1.4. Disadvantage

- Rapid Disintegrating tablet is hygroscopic in nature so must be keep in dry place.
- Some time it possesses mouth feeling.

- RDT requires special packaging for properly stabilization & safety of stable product. *(Kumari S et al)*

2. TECHNOLOGY FOR MOUTH DISSOLVING TABLETS

2.1. Conventional Techniques

2.1.1. Disintegrates addition

Disintegrate addition technique is one popular techniques for formulating Fast-dissolving tablets because of its easy implementation and cost-effectiveness. The basic principle involved in formulating Fast-dissolving tablets by disintegrates addition technique is addition of superdisintegrants in optimum concentration so as to achieve mouth dissolving along with the good mouth feel.

2.1.2. Molding

In this method, molded tablets are prepared by using water-soluble ingredients so that the tablets dissolve completely and rapidly. The powder blend is moistened with a hydro-alcoholic solvent and is molded into tablets under pressure lower than that used in conventional tablet compression. The solvent is then removed by air-drying. Molded tablets are very less compact than compressed tablets. These possess porous structure that enhances dissolution.

2.1.3. Freeze drying

A process in which water is sublimated from the product after freezing. Lyophilization is a pharmaceutical technology which allows drying of heat sensitive drugs and biological at low temperature under conditions that allow removal of water by sublimation. Lyophilization results in preparations, which are highly porous, with a very high specific surface area, which dissolve rapidly and show improved absorption and bioavailability.

2.1.4. Sublimation

The slow dissolution of the compressed tablet containing even highly water-soluble ingredients is due to the low porosity of the tablets. Inert solid ingredients that volatilize readily (e.g. urea, ammonium carbonate, ammonium bicarbonate, hexa methelene tetramine, camphor etc.) were added to the other tablet ingredients and the mixture is compressed into tablets. The volatile materials were then removed via sublimation, which generates porous structures. Additionally, several solvents (e.g. cyclohexane, benzene) can be also used as pore forming agents.

2.1.5. Spray-drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatins as supporting agents, mannitol as bulking agent, sodium starch glycolate or cross carmellose sodium as disintegrating and an acidic material (e.g. citric acid) and or alkali material (e.g. I sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

2.1.6. Mass-extrusion

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste.

2.1.7. Direct compression

Direct compression method is the easiest way to manufacture tablets. Conventional equipment, commonly available excipients and a limited number of processing steps are involved in direct compression. Also high doses can be accommodated and final weight of tablet can easily exceed that of other production methods. Directly compressed tablet's disintegration and solubilization depends on single or combined action of disintegrates, water soluble excipients and effervescent agent. *(Sharma S)*

2.2. Patented Technology

2.2.1. Flashtab technology

Prographarm laboratories have patented the Flashtab technology. Tablets prepared by this system consist of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation, and extrusion

spheronisation. All the processing utilized conventional tabletting technology.

2.2.2. Wowtab technology

Wowtab Technology is patented by "Yamanouchi Pharmaceutical Co." WOW means "Without Water ". In this process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide and granulated with a high mouldability saccharide and compressed into tablet.

2.2.3. Flash dose technology

Flash dose technology has been patented by "Fuisz". Nurofen meltlet, a new form of ibuprofen as melt-in-mouth tablets, prepared using flash dose technology is the first commercial product launched by" Biovail Corporation". Flash dose tablets consist of self binding shearform matrix termed as "floss". Shearform matrices are prepared by flash heat processing.

2.2.4 Orasolv technology

Orasolv technology has been developed by "CIMA" labs. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine is used to produce the tablets. The tablets produced are soft and friable and packaged in specially designed pick and place system.

2.2.5. Durasolv technology

Durasolv is the patented technology of "CIMA" labs. The tablets made by this technology consist of a drug, fillers and a lubricant. Tablets are prepared by using conventional tableting equipment and have good rigidity. These can be packed into conventional packaging system like blisters. Durasolv is an appropriate technology for products requiring low amounts of active ingredients.

2.2.6. Zydis technology

This technology involves softening the active blend using the solvent mixture of water soluble polyethylene glycol, using methanol and expulsion of softened mass through the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablets. The dried cylinder can also be used to coat granules of bitter tasting drugs and thereby masking their bitter taste. *(Chaudhari PD et al*)

3. MARKETED PRODUCTS

Table 1. Marketed product of RDT *(Chaudhari PD et al*

Brand name	Active ingredient	Application	company
Claritin® RediTabs®	Loratadine	Antihistamine	Scherig corporation
Feldene Melt®	Piroxicam	NSAIDs	Pfizer
Maxalt® -MLT®	Rizatritpan benzoate	Migrane	Merck
Pepeid® ODT	Femotidene	Anti-ulcer	Merck
Zyperxa®	Olazepine	Psychotropic	Eli Lilly
Zofran® ODT	Olandansetron	Antiemetic	Galaxo Smith kline
Resperdal® M-Tab™	Resperidone	Schizophrenia	Janssen
Zubrin™ (Pet drug)	Tepoxelin	Canine NSAIDs	Scherig corporation
Zelapar™	Selegiline	Parkinsons disease	Elanl Amarin corporation
Klonopin® wafer	Clonazepam	Sedation	Roche
Childrens Dimetapp® ND	Loratadine	Allergy	Wyeth consumer Healthcare
Imodium Istant Melts	Loperamide HCL	Antidiarrheal	Jannsen
Propulsid® Quicksolv ®	Cisapride Monohydrate	Gastrointestinal prokinetic Agent	Jannsen
Tempra Quicksolv®	Acetaminophen	Analgesic	Bristol-Mters squibb

Remeron® Soltab®	Mirtazapine	Anti-dipression	Organon Inc.

4. CRITERIA FOR DRUG SELECTION

- The ideal characteristics of a drug for in vivo dissolution from an RDT include:-
  - No bitter taste.
  - Dose lower than 20mg.
  - Small to moderate molecular weight.
  - Good stability in water and saliva.
  - Partially non-ionized at the oral cavities pH.
  - Ability to diffuse and partition into the epithelium of the upper GIT.
  - Ability to permeate oral mucosal tissue.
- Unsuitable drug characteristic for RDT:-
  - Short half-life and frequent dosing.
  - Very bitter or otherwise unacceptable taste because taste masking cannot be achieved.Required controlled or sustained release. *(C. Kumaresan)*

5. SUPER DISINTEGRANTS USED IN RDT_S

As day's passes, demand for faster disintegrating formulation is increased. So, pharmacist needs to formulate disintegrants i.e. Superdisintegrants which are effective at low concentration and have greater disintegrating efficiency and they are more effective intragranularly.

This superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

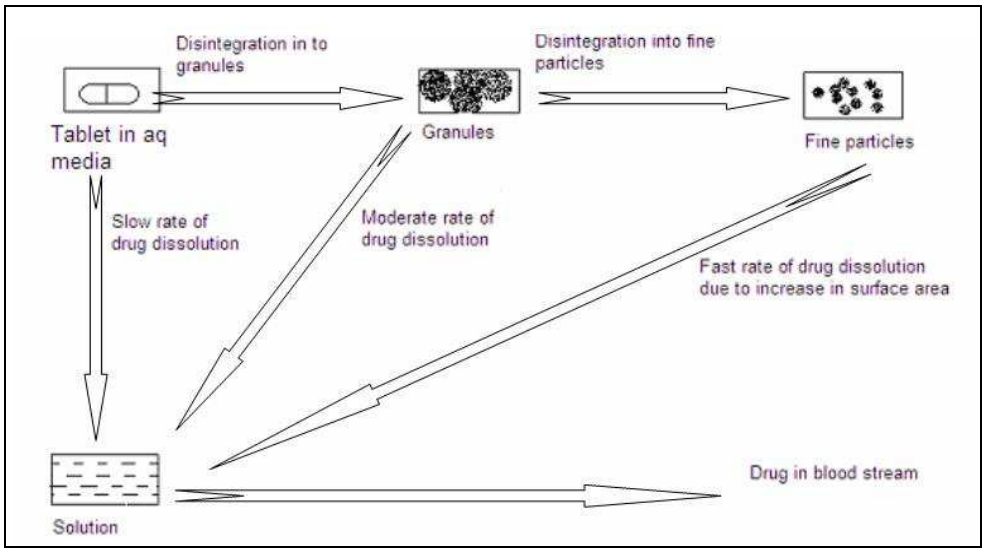

Figure1. Mechanism of tablet disintegration

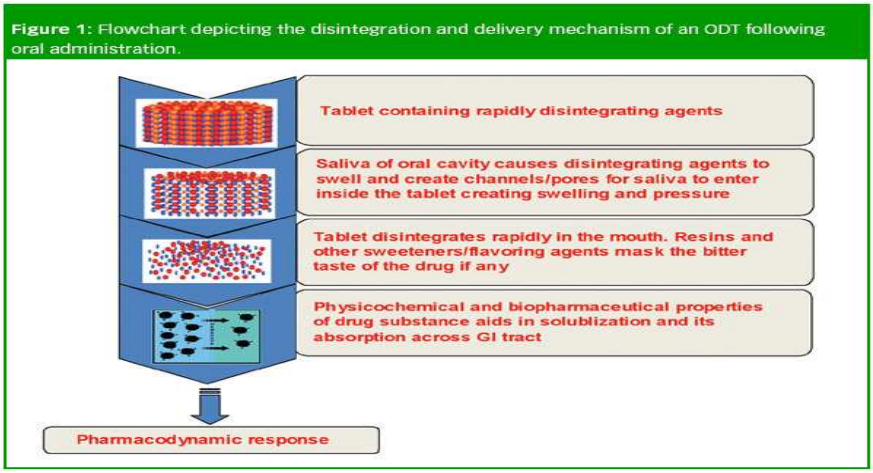

Figure2. Delivery mechanism of RDT

Various types of Super disintegrants used are as follows :

- ✓ Crosspovidone
- ✓ Microcrystalline cellulose
- ✓ Sodium starch glycollate
- ✓ Sodium carboxy methyl cellulose or cross carmelose sodium
- ✓ Pregelatinzed starch
- ✓ Calcium carboxy methyl cellulose
- ✓ Modified corn starch. Sodium starch glycollate has good flowability than crosscarmellose sodium.

Factors to be considered for selection of superdisintegrants:

- ✓ It should produce mouth dissolving when tablet meets saliva in the mouth
- ✓ It should be compactable enough to produce less-friable tablets.
- ✓ It can able to produce good mouth feel to the patient. Thus, small particle size are preferred to achieve patient compliance.
- ✓ It should has good flow since it improve the flowability of the total blend. *(Kumari S et al, Solanki AB et al)*

6. PREFORMULATION STUDIES

6.1. Bulk Density

Apparent bulk density was determine by pouring the 5 gram of powder into a 100 ml granulated cylinder. The bulk volume (V) poured drug was determined. The bulk density was calculated using the formula. *(Patel SS et al)*

$$\rho_b = M / V$$

Where : ρ_b - bulk density.

M- is the weight of powder,

V- is the volume of powder.

6.2. Tapped Density

Weight 5 g. of powder and placed in a measuring cylinder. Measuring cylinder containing known mass (5 gm) of powder was tapped for 100 times or fixed time. The minimum volume (V_t) occupied was measured. The tapped density was calculated using following formula. *(Patel SS et al)*

$$\rho_t = M / V_t$$

6.3. Compressibility Index

The simplest way for measurement of free flow of powder is compressibility, a indication of the ease with which a material can be induced to flow is given by Compressibility Index. The value below 15% indicates a powder with give rice to good flow properties, whereas above 25% indicate

poor flowability. Which is calculated follows. *(D. Bhowmik et al)*

$$\% \text{ C.I.} = \rho_t - \rho_b / \rho_t \times 100$$

Table 2. Relationship between % compressibility and flow ability

% Compressibility	Flow ability
5 – 12	Excellent
12 – 16	Good
18 – 21	Fair Passable
23 – 35	Poor
33 – 38	Very Poor
< 40	Very Very Poor

6.4. Hausner ratio

Hausner ratio is an indirect index of ease of powder flow. Hosner ratio is the ratio of tapped density to bulk density. Lower the value of Housner ratio better is the flow property. Powder with Housner ratio less than 1.18, 1.19, 1.25, 1.3- 1.5 and greater the 1.5 indicate excellent, good, passable, and very poor, respectively. It is calculated by following formula. *(Patel SS et al)*

$$\textbf{Hausner ratio} = \rho_b / \rho_t$$

6.5. Porosity

Percent relative porosity (ε) was obtained using the relationship between apparent density (ρ_{app}) and true density (ρ_{true}) which is calculated by following formula. *(O.M. Javier et al)*

$$\varepsilon = (1 - \rho_{app} / \rho_{true}) \times 100$$

6.6. Voide Volume

Voide volume(V) was obtained by difference between bulk volume(V_b) and tapped volume (V_p).Voide volume can be calculated by following formula- *(Sinko. J and Patrick Martins)*

$$V = V_b - Vp$$

6.7. Angle of repose

The angle of repose was determined using funnel method. Funnel that can be fit vertically with stand at 6.3 cm. height. The opening end of funnel are closed with thumb until drug are poured. The 5 gm of powder was poured into funnel that can be raised vertically until a maximum cone hight (h) was obtained. Radius of the heap (r) was measured and the angle of repose (θ) was calculated using the formula. *(Patel SS et al)*

$$\theta = \text{Tan}^{-1} (h / r)$$

Table 3. Angle of repose as an indication of powder flow properties

Sr. No	Angle of Repose (°)	Type of Flow
1	< 20	Excellent
2	20 – 30	Good
3	30 – 34	Passable
4	> 34	Very Poor

7. EVALUATION

7.1. Uniformity of weight

I.P. procedure for uniformity of weight was followed, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity. *(D. Bhowmik et al)*

Table 4.Weight variation specification as per IP

Average Weight of Tablet	% Deviation
80 mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

7.2. Thickness

Tablet thickness can be measured using a simple procedure. 5 tablets were taken and their thickness was measured using Varnier calipers. *(Shaikh S et al)*

7.3. Hardness

It is the force required to break a tablet by compression in the radial direction, it is an important parameter in formulation of RDTs because excessive crushing strength significantly reduces the disintegration time. In the present study the crushing strength of the tablet was measured using Pfizer hardness testers. An average of three observations is reported. *(Panigrahi R)*

7.4. Disintegration time

The test was carried out on 6 tablets using the apparatus specified in I.P.-1996 distilled water at 37ºC ± 2ºC was used as a disintegration media and the time in second taken for complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds. *(Mahaveer Pr Khinchi)*

7.5. In-vitro drug release

The development of dissolution methods for RDTs is comparable to the approach taken for conventional tablets, and is practically identical. Dissolution conditions for drugs listed in a pharmacopoeia monograph, is a good place to start with scouting runs for a bioequivalent RDT. Other media such as 0.1N HCl and buffers (pH - 4.5 and 6.8) should be evaluated for RDT much in the same way as their ordinary tablet counter parts.

The USP 2 Paddle apparatus is used for this purpose which is the most suitable and common choice for orally-disintegrating tablets, with a paddle speed of 50 rpm commonly used. Typically the dissolution of RDT is very fast when using USP monograph conditions; hence slower paddle speeds may be utilized to obtain a profile. The USP 1 Basket apparatus may have certain applications but sometimes tablet fragments or disintegrated tablet masses may become trapped on the inside top of the basket at the spindle where little or no effective stirring occurs, yielding irreproducible dissolution profiles. *(Mahaveer Pr Khinchi)*

7.6. Friability test

Friability of the tablets was determined using Roche friability (Electrolab, Mumbai). This device subjects the tablets to the combined effect of abrasions and shock in a plastic chamber revolving at 25 rpm and dropping the tablets at a height of 6 inches in each revolution. Preweighed sample of tablets was placed in the friabilator and were subjected to 100 revolutions. Tablets were de dusted using a soft muslin cloth and reweighed. The friability (f) is given by the formula.

$$f = (1- W0 / W) \times 100$$

Where, W0 is weight of the tablets before the test and W is the weight of the tablet after the test. *(Modasiya MK et al)*

7.7. In-vitro dispersion time test

To determine dispersion time 10 ml measuring cylinder was taken in which 6 ml distilled water was added and tablet was dropped in it. Time required for complete dispersion was determined. *(Shaikh S et al)*

7.8. Wetting time

Five circular tissue papers of 10 cm diameter are placed in a petridish with a 10 cm diameter. Ten millimeters of water-containing Eosin, a water-soluble dye, is added to petridish. A tablet is carefully placed on the surface of the tissue paper. The time required for water to reach upper surface of the tablet is noted as a wetting time. *(Shaikh S et al)*

7.9. Water absorption ratio

A piece of tissue paper folded twice was placed in a small Petri dish containing 6 ml of water. A tablet was put on the paper & the time required for complete wetting was measured. The wetted tablet was then weighed. Water absorption ratio (R), was determined using following equation,

$$R = 10 (W_a / W_b)$$

Where- W_b is weight of tablet before water absorption & W_a is weight of tablet after water absorption. *(Mahaveer Pr Khinchi)*

7.10. Accelerated Stability study

The Orally disintegrating tablets are packed in suitable packaging and stored under the following conditions for a period as prescribed by ICH guidelines for accelerated studies.

(i) 40 ± 1 °C
(ii) 50 ± 1°c
(iii) 37 ±1 ° C and

Relative Humidity= 75% ± 5%

The tablets were withdrawn after a period of 15 days and analyzed for physical characterization (Visual defects, Hardness, Friability, Disintegrations, and Dissolution etc.) and drug content. The data obtained is fitted into first order equations to determine the kinetics of degradation. Accelerated stability data are plotting according Arrhenius equation to determine the shelf life at 25 ° C. *(Mahaveer Pr Khinchi)*

7.11. Packaging

Packaging special care is required during manufacturing and storage to protect the dosage of other fast-dissolving dosage forms. Quick-dispersing and/or dissolving oral delivery systems, the system can be packaged using various options, such as single pouch, blister card with multiple units, multipleunit dispenser, and continuous roll dispenser, depending on the application and marketing objectives. *(Kumari S et al)*

8. CONCLUSION

Rapid dissolving Tablets is the general form of nomenclature for tablets that disintegrate rapidly or instantly in the oral cavity. RDT_s have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. RDTs can be prepared in different ways and product performance depends upon the drug suitability and excipients selections in the delivery system. In combination with other technologies such as modified release and microencapsulation, RDTs will continue to provide enhanced commercial and therapeutic benefits. RDT is a growing technology, offering considerable benefits for lifecycle management[16], development timelines, patient convenience and market share. By paying close attention to advances in technologies, pharmaceutical companies can take advantage of RDTs for product line extensions or for first-to-market products. With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for RDTs in the days to come. The successful marketed RDTs have good taste and rapid release properties. With rapid acceptance of RDTs by patients and pharmaceutical companies, the market for this dosage form is promising, and the product pipeline continues to grow rapidly.

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