



A Review Article on Fast Dissolving Tablet of Rosuvastatin

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ABSTRACT

The pharmaceutical industry is showing a lot of interest in fast-dissolving drug delivery systems because they provide a number of advantages over traditional dosage forms, including rapid drug disintegration and water-free salivary dissolution. A competitive HMG-CoA inhibitor called rosuvastatin calcium is used to treat dyslipidemia, the main condition that causes CVDs. To boost the drug's bioavailability, the GI tract should absorb it gradually and partially. This work demonstrated how to manufacture rosuvastatin FDTs to improve solubility and speed up the rate of dissolution. Marketed study of rosuvastatin percentage amount of dosage forms available in market is also discussed.

KEYWORDS: Rosuvastatin, Fast dissolving tablet, HMG-CoA reductase inhibitor, orodispersible tablet, marketed formulations

INTRODUCTION

The trademark of the modern era is to development of ever-new dose forms that fulfil the patient's demands. To increase patient compliance, efforts are being undertaken to improve safety, effectiveness, and bioavailability with the least amount of adverse effects and dosage frequency.^[1] In the pharmaceutical business, around 40% of newly created medications are poorly soluble in water when they are introduced to generate novel dosage forms, This tends toward low levels of oral absorption and bioavailability and decreases their dissolution in the gastrointestinal system. Various methods have been employed to address these issues and improve the medications' solubility and bioavailability.^[2,3]

Fast dissolving tablets are an innovative form of drug administration that, whether or not water is consumed, dissolve, disintegrate, or spread the API in saliva in a matter of seconds. The absorption and start of the therapeutic action happen more quickly the faster the medication dissolves in the solution. Certain medications may have a higher bioavailability due to oral drug absorption or pre-gastric drug absorption via saliva that travels down into the stomach. Both natural and synthetic Superdisintegrants, such as mucilage, crospovidon, sodium starch glycolate (primogel), cross-linked carboxymethyl cellulose (croscarmellose), poly vinyl pyrrolidone, etc., offer rapid tablet disintegration and make it easier to build delivery systems with the desired characteristics.^[4]

Rosuvastatin (*Fig-1*) according to BCS class II drug rosuvastatin calcium (RST) has a high permeability and poor solubility. It is a 3-hydroxy-3-methyl glutaryl CoA (HMG CoA) reductase inhibitor that is poorly soluble in water. This enzyme is a strong lipid-lowering component and a hypolipidemic drug 10. It catalyzes the conversion of HMG CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.^[5]

The decision was made to formulate Rosuvastatin fast-dissolving tablets by improving its solubility through the solid dispersion method, which may be a better option for immediate effect, uniform plasma concentration profile, enhanced bioavailability, and patient compliance with sufficient therapeutic benefits. These decisions were made based on the aforementioned physicochemical and biopharmaceutical properties.

The medicine needs a drug delivery method to improve absorption because it has limited bioavailability due to partial absorption and poor solubility in water.

Water soluble, physiologically inert, nontoxic, and thermally stable at melting temperature are all characteristics of PEG 4000. These characteristics make it perfect for creating solid dispersions.^[6]

❖ Drug profile



Fig 1: Chemical Structure Of Rosuvastatin

Background: The lipid-lowering medicine rosuvastatin (*fig: 1*), also marketed under the trade name Crestor, is a member of the statin drug class. Statins work by preventing the liver's natural synthesis of cholesterol, which lowers the risk of cardiovascular disease and manages increased lipid levels. More precisely, statin drugs competitively block the activity of the enzyme HMG-CoA Reductase.^[7]

Chemical name: (3R,5S,6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid also known as a dihydroxy monocarboxylic acid.

Chemical Formula: C₂₂H₂₈FN₃O₆S

Molecular weight : 481.539 g/mol

Synonyms:

(3R,5S,6E)-7-(4-(4-fluorophenyl)-6-(1-methylethyl)-2-(ethyl(methylsulfonyl)amino)-5-pyrimidinyl)-3,5-dihydroxy-6-heptenoic acid

(3R,5S,6E)-7-{4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl}-3,5-dihydroxyhept-6-enoic acid

Rosuvastatin, Rosuvastatina

Brand Names: *Crestor, Ezallor, Roszet*

Generic Name: Rosuvastatin

Associated Therapies: Lipid-Lowering Therapy

Primary Prevention of Cardiovascular Diseases

Mechanism of action

A competitive inhibitor of HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase, rosuvastatin is a statin drug that facilitates the conversion of HMG-CoA to mevalonate, an early rate-limiting step in the manufacture of cholesterol.²⁴ Rosuvastatin mainly affects the liver, where lower liver cholesterol levels cause the liver's low density lipoprotein (LDL) receptors to become more highly expressed, increasing the liver's ability to absorb LDL. Additionally, very low density lipoprotein (VLDL) production in the liver is inhibited by rosuvastatin.^[8,9]

❖ CONCEPT OF FAST DISSOLVING TABLET (FDTs)

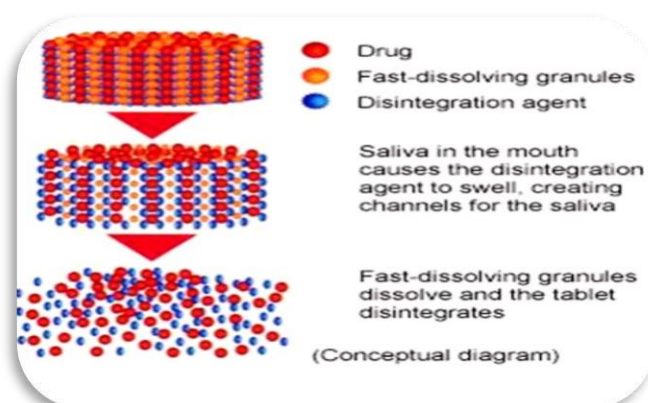


Fig 2: concept of fast dissolving tablet

Definition as per (USFDA)

“A fast dissolving tablets (FDTs) is a solid dosage form that contains a medication or active ingredient that dissolves quickly typically in a few seconds when put on the tongue, according to the United States Food and Drug Administration (FDA). “

Fast dissolving tablets are sometimes referred to as rapid disintegrating, melt-in-mouth, Orodispersible, rapid dissolving, porous, and mouth-dissolving tablets. Water is not necessary for the fast-dissolving tablets to dissolve or disintegrate in the mouth.^[10,11] It has been determined that a quicker dissolving, absorption (for the unionized form of the medication alone), and start of action are all related. When saliva travels down into the stomach, some medications are absorbed from the pharynx, esophagus, and mouth cavity. As a result, the drug's bioavailability is noticeably higher than that of standard tablet dosage form.^[12]



Fig :3 fast dissolving tablet

❖ IDEAL CHARACTERISTICS OF FDTs ^[13]

The optimal qualities of ODTs that set them apart with conventional dose forms includes,

1. It doesn't require water and should dissolve or disintegrate in the mouth in just a few of seconds.
2. A substantial drug loading.
3. Harmonious with additional excipients and flavor concealing.
4. It should be transportable and not break easily.
5. After oral dosage, leave very little or no residue in the mouth.



6. Show minimal sensitivity to changes in temperature and humidity in the surroundings.
7. Feel good in the mouth.
8. Flexible and receptive to nominally expensive production, processing, and packaging equipment.

ADVANTAGES OF FAST DISSOLVING TABLETS ^[14,15]

1. Water is not required for swallowing a medicine.
2. Patients with mental disabilities, the elderly, and children can all get FDTs with comfort.
3. Proper dose in comparison to liquids.
4. The medication dissolves and absorbs quickly, providing a quick start to action.
5. Drug bioavailability is enhanced because saliva travels down the stomach's digestive tract to absorb some medications from the mouth, throat, and oesophagus.
6. Cheaper in terms of transportation and administration than liquid medicine.
7. A reduced first pass metabolism results in increased bioavailability, a lower dosage, and fewer adverse effects.
8. Providing better safety.
9. Promotes large drug loading.

LIMITATIONS OF FDTs ^[16,17]

1. The mechanical strength of the tablets is one of the main disadvantages of FDTs.
2. FDT are soft, molded metrics that are extremely porous and compressible, making them fragile and difficult to handle in tablets with low compression.
3. It is challenging to develop medications with bad tastes like FDT; extra care must be taken before formulating such a drug.
4. For some tablet formulations, dry mouth caused by reduced salivary flow may not be a good fit.
5. The rate at which the saliva solution is absorbed and the total bioavailability.
6. Stability of drugs and dose forms.

THE NEED OF FDTS DEVELOPMENT ^[18,19]

1. Individuals who struggle with chewing or swallowing solid dose forms.
2. Patient's noncompliance because they are afraid of choking.
3. Two really old depressed people who might not be able to swallow the solid dose forms.
4. Those suffering from depression who are very old and might not be able to stomach the solid dose forms.
5. An eight-year-old allergy sufferer would prefer a more portable dosing form than antihistamine syrup.
6. An elderly woman receiving radiation treatment for breast cancer could feel too queasy to take her H2-blocker.



❖ APPROACHES FOR FAST DISSOLVING TABLETS ^[20,21]

The tablet's fast-dissolving ability can be attributed to the water entering the tablet matrix quickly, which causes the tablet to disintegrate quickly. Therefore, the fundamental methods for creating quickly dissolving tablets involve optimizing the tablet matrix's porous structure, adding the proper disintegrating agent, and utilizing highly water-soluble excipients in the formulation.

❖ CHALLENGES IN THE FORMULATION OF FDTs ^[22-27]

The disintegration time and mechanical strength

With excellent mechanical strength, ODT often disintegrates in less than a minute. Numerous ODTs are brittle, and there's a good probability that one of these tablets may shatter in transit, during packaging, or when patients handle it. Delaying the disintegration period by increasing the mechanical strength makes perfect sense. As a result, both criteria should be taken seriously.

Palatability

It becomes quite difficult to formulate oral disintegrating tablets when the medicine should be in a taste-masked form because the majority of pharmaceuticals are not appetizing. The active chemicals in ODTs are released into the patient's mouth cavity and come into touch with their taste buds. As a result, taste masking of the medications becomes essential to patient compliance.

mouth sensation

mouth sensation that a tablet produces as it is chewed or dissolves. Smooth texture and a calming or cooling effect (like Pearlithol) are desired.

Gritfulness

Particles larger than 50µm might have a grainy sensation. It is not ideal to have a gummy or grittier feel (such as calcium carbonate).

After-effect

side effects include numbness in some areas or throughout the lips and tongue, as in the case of the bitter antihistaminic Promethazine HCl. Another consequence is aftertaste. For example, a high sugar content might produce an aftertaste that is harsh.

The ability to hygroscopic

Because they are hygroscopic, a number of oral disintegrating dosage forms are unable to retain their physical integrity in typical humidity and temperature ranges. As a result, they need to be protected against damp, which necessitates specific product packaging.

Price

Regarding the ultimate product's cost, the manufacturing process used to create an ODT should be deemed appropriate. Techniques like Zydys and Orasolv, which call for unique production and packaging techniques, significantly raise the cost.

Tablet dimensions (size)

The size of the medication affects how easy it is to take. According to reports, tablets with a size between 7 and 8 mm are the simplest to swallow, while tablets bigger than 8 mm are the easiest to manage. Therefore, it is challenging to make a pill that is both manageable and simple to consume.

❖ Marketed Formulations of Rosuvastatin

- Oral dosage form's ^[28]

Tablets

Immediate-release Tablets: Rosuvastatin pills with immediate release are made without a special coating or delayed release mechanisms, so the active medication dissolves and releases promptly for speedy absorption.

Extended-release Tablets: Compared to immediate-release formulations, rosuvastatin tablets with extended-release technology allow for less frequent dosage because the active ingredient is released gradually and continuously over an extended period of time.



Fig 4: Immediate-release Tablets



Fig 5: Extended-release Tablets

Capsules

Rosuvastatin is included in capsules, an oral dosage form type, which is a rigid gelatin shell.



Fig 6 : capsule

- **Parenteral Dosage form** ^[29]

Rosuvastatin is injected into muscle tissue rather than administered intravenously.



Fig 7 : parenteral solution

Intramuscular suspensions: Rosuvastatin intramuscular suspensions are intended for direct injection into muscles, contrasting with intravenous suspensions that go straight into the bloodstream.

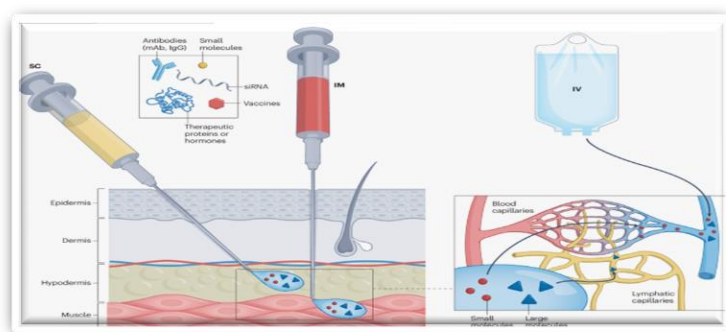


Fig 8 : intramuscular injection

- **Transdermal patches** ^[30]

Patches with a matrix structure are used for delivering rosuvastatin through the skin. The drug is evenly spread within a polymeric matrix, ensuring consistent and extended release of the medication.

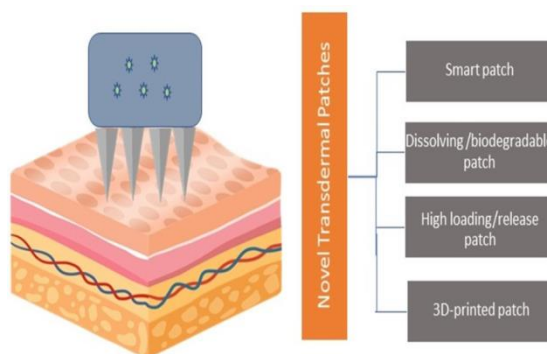


Fig 9 : patches



❖ Various drugs which can used in FDTs

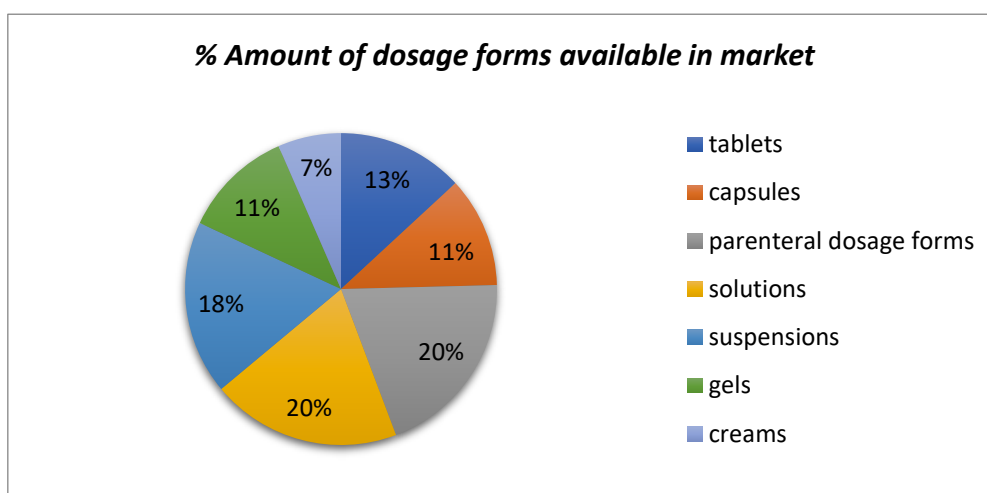
Table:1 examples of drugs which used in FDTs

| Sr.no | Category | Drug |
|-------|---|---|
| 1 | Analgesics and Anti-inflammatory agents | Piroxicam, Ibuprofen, Ketoprofen, Sulindac, Phenylbutazone, Naproxen, Indomethacin. |
| 2 | Statin's | Atorvastatin, fluvastatin, Lovastatin, Pravastatin, Rosuvastatin, Simvastatin, |
| 3 | Antiepileptic | Carbamazepine, Methsuximide, Phenytoin, Primidone, Phenobarbitone, Valproic acid, |
| 4 | Antimalarial | Chloroquine, Mefloquine, Proguanil, Pyrimethamine |

❖ Rosuvastatin Formulations in the Market ^[28-30]

Table 2: Rosuvastatin Formulations in the Market

| Sr.No | Routs of administration | category | Sub-category | % In market |
|-------|-------------------------|-------------|---------------------------------|-------------|
| 1. | Oral Dosage Forms | Tablets | Immediate-release Tablets(FDTs) | 25% |
| | | | Extend release tablet | 33.33% |
| | | Capsule | - | 25% |
| 2. | Parenteral Dosage Forms | Solutions | Intravenous Solutions | 50% |
| | | Suspensions | Intravenous Suspensions | 50% |
| 3. | Topical Dosage Forms | Gels | Hydrogel Nasal Gels | 33.33% |
| | | | Hydrophilic Creams | 33.33% |
| | | Creams | | |



Percentage-wise contribution of Dosage forms in market

❖ TRADITIONAL METHODS USED TO PRODUCE FAST DISSOLVING DRUG DELIVERY SYSTEM FDDs ^[31-35]

Manufacturing techniques used for fast dissolving tablets have talked about the seven main methods that are frequently employed to manufacture these pills.

A. Direct compression

The simplest and cheapest method for making tablets with enough structural strength is this one. The most popular method is direct compression (DC), which is chosen for its ease of usage, speed, economy, and stability issues.

It's the simplest method for producing tablets. Direct compression involves standard tools, widely accessible excipients, and a minimal number of processing stages.



Advantages of Direct Compression

1. The fundamental particles are immediately responsible for disintegration because there is no aggregation step involved.
2. Since crucial processes like granulation and drying are not employed, a granulator and dryer are not necessary.
3. Sturdy pills that are manageable and not brittle
4. Pleasant flavor and a creamy mouthfeel.
5. Less expensive

B. Disintegrant addition

The disintegrant addition technique is a widely used method for creating fast-dissolving tablets due to its affordability and ease of usage. The fundamental idea behind the disintegrant addition approach for creating fast-dissolving tablets is to add superdisintegrants at the right concentration to provide both a quick disintegration and a pleasant mouthfeel.

C. Freeze drying

A pharmaceutical technique also called lyophilization enables the low-temperature drying of biological materials and heat-sensitive medications in an environment that permits the sublimation of water.

D. A spray drying

Spray drying can result in tiny, quickly dissolving powders that are extremely porous. Hydrolyzed and non-hydrolyzed gelatins are used as supporting agents in the formulations, along with mannitol for bulking, sodium starch glycolate or cross carmellose sodium for disintegrating, and an acidic (like citric acid) or alkali (like sodium bicarbonate) material to improve disintegration and dissolution.

E. Sublimation

The limited porosity of the tablets is the reason for the delayed dissolving of the compressed tablet, even with components that are highly water soluble. Sublimation was then used to eliminate the volatile components, creating porous structures in the process.

F. Moulding

This process involves creating molded tablets with chemicals that dissolve quickly and fully in water. After that, the solvent is eliminated by air-drying.

G. Mass Extrusion

Using a solvent combination of methanol and water-soluble polyethylene glycol, this method softens the active blend.

❖ A FUTURE PROSPECT ^[36-39]

In the pharmaceutical business, oral administration is now the gold standard since it is seen to be the safest, most practical, cost-effective, and patient-complies drug delivery route. The purpose of this tablet format is to enable the administration of an oral solid dosage form when no fluids or water is consumed. These pills easily dissolve or break down in saliva, usually in less than 60 seconds.

Using technology created by pharmaceutical businesses including Cardinal Healthcare, Janssen Pharmaceutical, Bioavail, and Eurand, Yamanouchi, a variety of FDTs are commercially accessible for human usage. However, these methods either employ traditional tableting techniques that result in longer than expected disintegration and still require specialized packaging.

The oral drug delivery industry was valued at \$35 billion in 2006 and is expected to grow at a compound annual growth rate of 10% to reach \$52 billion by 2010. With a predicted CAGR of 17% through 2010, the ODT, flavor disguised, and micro emulsion



formulation categories account for 22% of this total.

This market area has a clear possibility for the introduction of new, improved oral solutions.

❖ CONCLUSION

The oral dispersible tablet was developed to address some issues with the traditional solid dose form (tablet and capsule), such as swallowing difficulties.

Because they both have trouble swallowing regular pills, the juvenile and geriatric populations are the main ones whose issues ODTs may readily address. Because it absorbs quickly from the mouth to the GIT as saliva passes, it also results in improved effectiveness, bioavailability, rapid beginning of action, and enhanced patient compliance.

Their unique benefits like the ability to administer them anywhere, at any time, and without the need for water have led to a rise in patient compliance in the busy world of today. Today, Oral dispersible tablets are more widely available as over-the-counter products for the treatment of allergies, cold and flu symptoms. Future possibilities for improvements in Rapid disintegrating and drug delivery are bright, but the technology is still relatively new.

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