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DESIGN AND DEVELOPMENT OF LOVASTATIN MOUTH DISSOLVING TABLETS BY USING NOVEL SUPER DISINTEGRANTS

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Abstract:

Mouth dissolving tablets are a vital tool in keeping our children and elderly population healthy. Their ease of use and accurate dosing allow higher patient compliance and more reliable therapeutic effects. Superdisintegrants are the fundamental element contained in Mouth dissolving tablets and are responsible for their unique ability to quickly disintegrate and dissolve on the surface of the tongue without the use of any additional liquid. In order to determine the most effective type and optimal amount of superdisintegrants for orally disintegrating tablets manufactured by direct compression, the following tablet parameters were tested hardness, thickness, friability, disintegration time, and wetting time. Three superdisintegrants were tested, namely: Kyron T-314, Ac-Di-Sol, and Banana Powder and the most efficient superdisintegrant was selected based on the above mentioned studies. From the results obtained, it can be concluded that the tablet formulation (F3) showed the promising formulation also the hardness, friability, disintegration time and dissolution rate of prepared tablets were found to be acceptable according to standard limits.

Keywords: *Lovastatin, Kyron T-314, Ac-Di-Sol, Banana Powder and Mouth dissolving tablets.*

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INTRODUCTION:

The oral route of administration is considered as the most widely accepted route because of its convenience of self administration, compactness and easy manufacturing. But the most evident drawback of the commonly used oral dosage forms like tablets and capsules is difficulty in swallowing, leading to patients incompliance particularly in case of paediatric and geriatric patients, but it also applies to people who are ill in bed and to those active working patients who are busy or travelling, especially those who have no access to water.

For these reasons, tablets that can rapidly dissolve or disintegrate in the oral cavity have attracted a great deal of attention. Mouth disintegrating tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people. [1.]

An Mouth disintegrating tablet (MDT) is a solid dosage form that contains medicinal substances and disintegrates rapidly (within seconds) without water when placed on the tongue. The drug is released, dissolved, or dispersed in the saliva, and then swallowed and absorbed across the GIT. [2].

US FDA defined MDT tablets as "A solid dosage form containing medicinal substances which disintegrates rapidly usually within a matter of seconds, when placed upon the tongue".

Recently European Pharmacopoeia used the term 'Orodispersible tablet' as a tablet that is to be placed in the mouth where it disperses rapidly before swallowing.

Mouth disintegrating tablets are also called as mouth-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, orodispersible tablets, rapimelts, porous tablets, quick dissolving tablet[·] .

The US Food and Drug Administration responded to this challenge with the 2008 publication of Guidance for Industry: Mouth Disintegrating Tablets (Rosie et al., 2009).Three main points stand out in the final guidance:

- MDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the MDT tablet weight should not exceed 500 mg, although the combined influence of tablet weight, size, and component solubility all factor into the acceptability of an MDT for both patients and regulators.
- The guidance serves to define the upper limits of the MDT category, but it does not supersede or replace the original regulatory definition mentioned. In other words, disintegration within a matter of seconds remains the target for an MDT.

1.1. NEED TO DEVELOP MDT:[3-7]

The need for one of the non-invasive delivery system i.e., Mouth disintegrating tablets persists due to patients' poor acceptance of, and compliance with, existing delivery regimes, limited market size for drug companies and drug uses, coupled with high cost of disease management.

PATIENT FACTORS:

Mouth disintegrating dosage forms are particularly suitable for patients, who for one reason or the other; find it inconvenient to swallow tablets and capsules with an 8-oz glass of water. These include the following:

- Paediatric and geriatric patients who have difficulty in swallowing or chewing solid dosage forms.
- Patients who are unwilling to take solid preparation due to fear of choking.
- Very elderly patients who may not be able to swallow a daily dose of antidepressant.
- An eight-year old with allergies who desires a more convenient dosage form than antihistamine syrup
- A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2- blocker.
- A schizophrenic patient in an institutional setting who may try to hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic.
- A patient with persistent nausea, who may be journey, or has little or no access to water

EFFECTIVENESS FACTORS:

- Increased bioavailability and faster onset of action 0are a major claim of these formulations.
- Dispersion in saliva in oral cavity causes pregastric absorption from some formulations in those cases where drug dissolves quickly.
- Buccal, pharyngeal and gastric regions are all areas of absorption for many drugs**.**
- Any pregastric absorption avoids first pass metabolism and can be a great advantage in drugs that undergo a great deal of hepatic metabolism.

- Furthermore, safety profiles may be improved for drugs that produce significant amounts of toxic metabolites mediated by first-pass liver metabolism and gastric metabolism, and for drugs that have a substantial fraction of absorption in the oral cavity and pregastric segments of GIT.

MANUFACTURING AND MARKETING FACTORS:

- Developing new drug delivery technologies and utilizing them in product development is critical for pharmaceutical industries to survive, regardless of their size.
- As a drug nears the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form.
- A new dosage form allows a manufacturer to extend market exclusivity, unique product differentiation, value-added product line extension, and extend patent protection, while offering its patient population a more convenient dosage form.
- This leads to increased revenue, while also targeting underserved and under-treated patient populations.

1.2. MECHANISM OF ACTION OF MDT IN ORAL MUCOSA:[8-10]

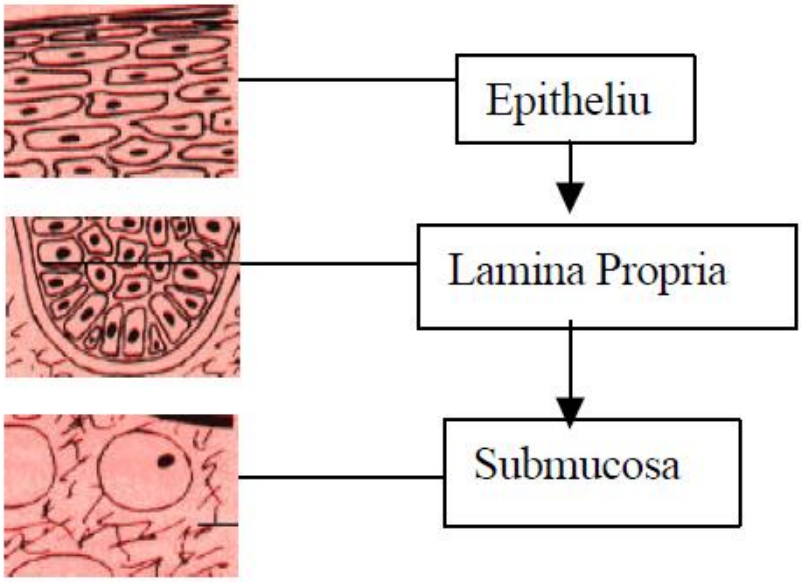

Fig: 1.1 Different layers of oral mucosa (Nehal Siddiqui *et al* .,2011)

MECHANISM OF ACTION: The MDT is placed upon patient's tongue or any oromucosal tissue. It instantly get wet by saliva due to presence of hydrophilic polymer and other excipients, then the tablet rapidly hydrates and dissolves to release the medication for oromucosal absorption.

1.3. ADVANTAGES OF MDTS:

Advantages of MDTs include:

- Ease of administration to geriatric, paediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.
- The MDTs do not need water for swallowing unlike conventional dosage forms. This is very convenient for patients who are travelling or do not have immediate access to water, and thus, provide improved patient compliance.
- Being unit solid dosage forms, provide luxury of accurate dosing, easy portability and manufacturing, good physical and chemical stability and an ideal alternative for paediatric and geriatric patients.
- Bioavailability of drugs is enhanced due to absorption from mouth, pharynx, and oesophagus.
- Pregastric absorption can result in improved bioavailability and because of reduced dosage, improved clinical performance through a reduction of unwanted effects.
- Rapid onset of therapeutic action as tablet is disintegrated rapidly along with quick dissolution and absorption in oral cavity.
- Good mouth feels, especially for paediatric patients as taste-masking technique is used to avoid the bitter taste of drugs.

- Minimum risk of suffocation in airways due to physical obstruction, when MDTs are swallowed, thus they provide improved safety and compliance with their administrations.
- Rapid drug therapy intervention is possible.
- Conventional processing and packaging equipments pleat disintegration in the mouth.[3]

1.4. LIMITATIONS TO MOUTH DISSOLVING TABLETS :

- Drugs with relatively larger doses are difficult to formulate into MDTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug.
- Patients who concurrently take anti cholinergic medications may not be the best candidates for MDTS.

METHODOLOGY:

Buffer preparation:

Preparation of 0.2 M Potassium dihydrogen orthophosphate solution: Accurately weighed 27.128 gm of monobasic potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water and mixed.

Preparation of 0.2 M sodium hydroxide solution: Accurately weighed 8 gm of sodium hydroxide pellets were dissolved in 1000 mL of distilled water and mixed.

Preparation of pH 6.8 phosphate buffer: Accurately measured 250 mL of 0.2 M potassium dihydrogen orthophosphate and 112.5 mL of 0.2 M NaOH was taken into the 1000 mL volumetric flask. Volume was made up to 1000 mL with distilled water.

Analytical method development for Lovastatin:

a) Determination of absorption maxima

A spectrum of the working standards was obtained by scanning from 200-400 nm against the reagent blank to fix absorption maxima. The λ_{max} was found to be 238 nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Lovastatin was dissolved in 100 mL of pH 6.8 phosphate buffer to give a concentration in 1mg/mL (1000µg/mL) 1 ml was taken and diluted to 100 ml with pH 6.8 phosphate buffer to give a concentration of 0.01 mg/ml (10µg/ml). From this stock solution aliquots of 0.5 ml, 1 ml, 01.5 ml, 2 ml, 2.5 ml, were pipette out in 10 ml volumetric flask and volume was made up to the mark with pH 6.8 phosphate buffer to produce concentration of 5, 10, 15, 20 and 25µg/ml respectively. The absorbance of each concentration was measured at respective (λ_{max}) i.e., 238 nm.

Formulation development:

Drug and different concentrations of super disintegrants (Kyron T-314, Ac-Di-Sol and Banana Powder) and required ingredients were accurately weighed and passed through a 40-mesh screen to get uniform size particles and mixed in a glass motor for 15 min.

- The obtained blend was lubricated with magnesium stearate and glidant (Talc) was added and mixing was continued for further 5 min.
- The resultant mixture was directly compressed into tablets by using punch of rotary tablet compression machine. Compression force was kept constant for all formulations.

Table 7.1: Formulation table showing various compositions

INGREDIENTS (MG)	FORMULATION CODES								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lovastatin	20	20	20	20	20	20	20	20	20
Kyron T-314	25	50	75	-	-	-	-	-	-
Ac-Di-Sol	-	-	-	25	50	75	-	-	-
Banana Powder	-	-	-	-	-	-	25	50	75
Sodium saccharin	20	20	20	20	20	20	20	20	20
Talc	5	5	5	5	5	5	5	5	5
Mg stearate	4	4	4	4	4	4	4	4	4
MCC	126	101	76	126	101	76	126	101	76
Total Weight (mg)	200	200	200	200	200	200	200	200	200

RESULTS AND DISCUSSION:

Preparation of Calibration Curve of Lovastatin:

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of Y= 0.059 X-0.002. Hence Beer-Lambert's law was obeyed.

Table 8.1 : Calibration curve data of Lovastatin in pH 6.8 phosphate buffer

Concentration	Absorbance
0	0
5	0.181
10	0.327
15	0.468
20	0.611
25	0.758

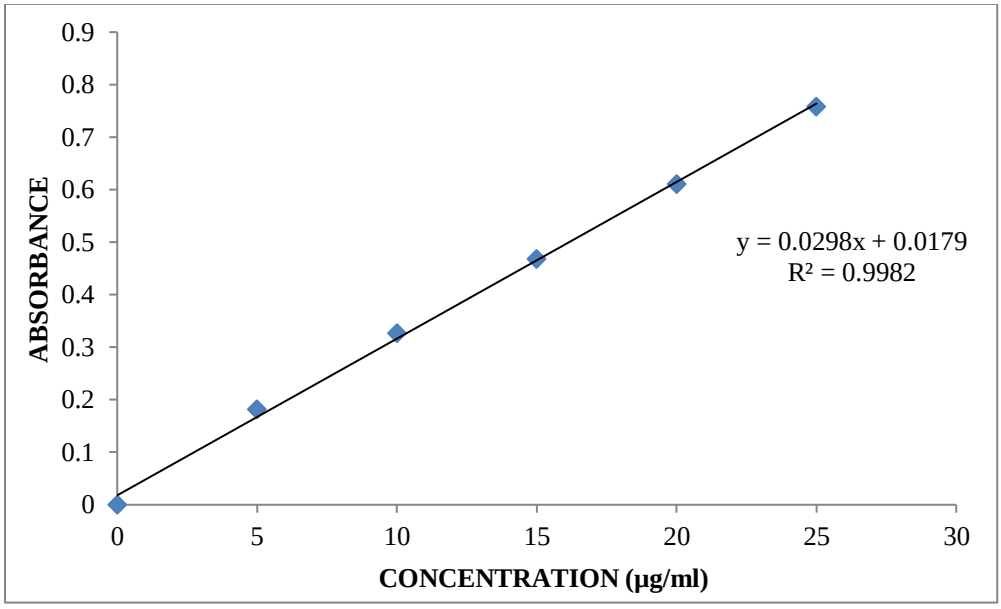

Fig 8.1: Standard curve of Lovastatin

Evaluation of pre-compression parameters of powder blend

Table 8.2: Evaluation of pre-compression parameters of powder blend

Formulation Code	Angle of Repose	Bulk Density(gm/mL)	Tapped Density (gm/mL)	Carr's Index(%)	Hausner's Ratio
F1	25.92±0.04	0.326±0.076	0.354±0.06	7.998±0.04	1.086±0.03
F2	24.56±0.02	0.37±0.04	0.408±0.03	9.524±0.07	1.095±0.03
F3	26.93±0.06	0.350±0.065	0.382±0.02	8.444±0.02	1.090±0.02
F4	27.25±0.04	0.37±0.04	0.387±0.02	5.541±0.06	1.045±0.05
F5	27.82±0.04	0.272±0.076	0.314±0.03	13.33±0.04	1.153±0.08
F6	26.93±0.03	0.324±0.05	0.337±0.03	8.76±0.04	1.041±0.03
F7	27.82±0.04	0.382±0.087	0.404±0.06	5.547±0.03	1.047±0.04
F8	25.07±0.06	0.236±0.06	0.266±0.04	11.428±0.03	1.129±0.05
F9	24.39±0.02	0.259±0.054	0.286±0.02	9.406±0.02	1.103±0.03

- For each formulation blend of drug and excipients were prepared and evaluated for various pre compression parameters described earlier in methodology chapter.

- The bulk density of all formulations was found in the range of 0. 0.236±0.06 - 0.382±0.087 and tapped densiy was in the range of 0.266±0.04 - 0.408±0.03
- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

Evaluations of post compression parameters of Lovastatin mouth dissolving tablets

Table 8.3: Evaluation of post compression parameters of Lovastatin Mouth dissolving tablets

Formulation codes	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)
F1	198.47	3.9	0.54	3.96	98.12
F2	200.01	3.4	0.46	3.89	99.47
F3	199.36	3.6	0.65	3.45	96.35
F4	195.47	3.0	0.47	3.58	100.02
F5	200.03	3.9	0.51	3.70	98.41
F6	199.98	4.1	0.63	3.46	96.54
F7	199.63	3.8	0.42	3.24	98.68
F8	198.21	3.5	0.50	3.99	97.42
F9	199.20	3.2	0.28	3.54	99.67

Weight variation and Thickness: All the formulations were evaluated for uniformity of weight using electronic weighing balance and the results are shown above. The average tablet weights of all the formulations were noted down.

Hardness and friability: All the Mouth Dissolving formulations were evaluated for their hardness using Monsanto hardness tester and the results are shown above. The average hardness for all formulations was found to be between (3.0 – 4.1) kg/cm^2 which was found to be acceptable. Friability was determined to evaluate the ability of the tablets to with stand the abrasion during packing, handling and transpoting. All the Mouth dissolving formulations were evaluated for their percentage friability using Roche friabilator and the results are shown above. The average percentage friability for all the formulations was between 0.28 – 0.65 which was found to be within the limit.

Drug content: All formulations were evaluated for drug content according to the procedure described in methodology section and the results were shown above. The assay values for all formulations were found to be in the range of (96.35 – 100.02). According to IP standards the tablets must contain not less than 95% and not more than 105% of the stated amount of the drug. Thus, all the Mouth dissolving formulation complies with the standards given in IP.

Table 8.4: Evaluation of post compression parameters of Lovastatin mouth dissolving tablets

Formulation	Disintegration time*(seconds)	Wetting time* (seconds)	*In vitro* dispersion time*(sec)	% Water absorption ratio*
F1	48	51	48	94
F2	36	43	30	98
F3	28	36	24	99
F4	40	55	51	95
F5	36	45	38	97
F6	30	39	32	99
F7	42	60	56	98
F8	38	52	44	98
F9	30	43	32	97

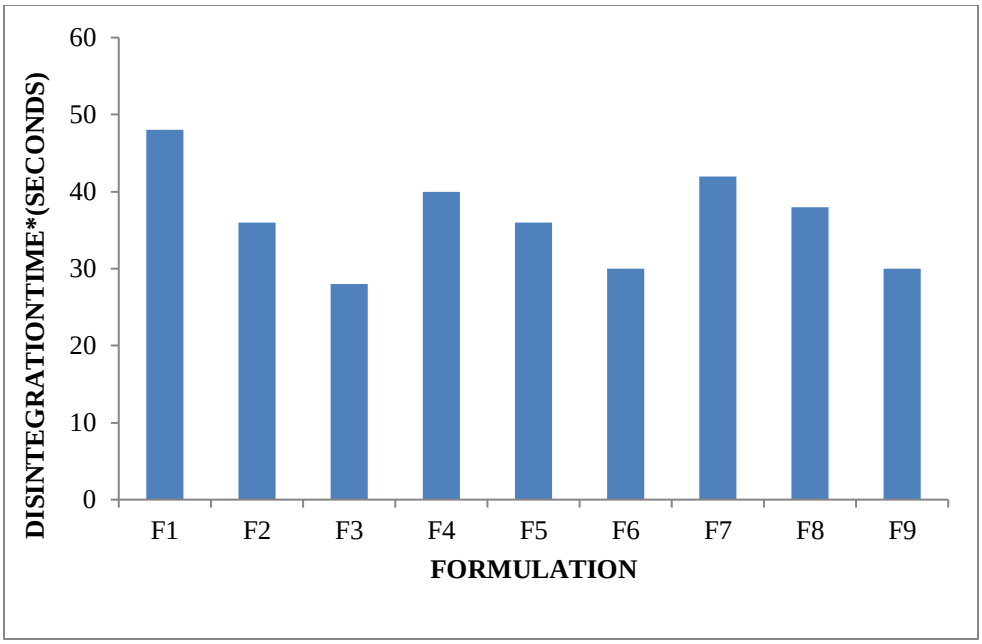

Figure 8.2 : *In vitro* Disintegration time graph

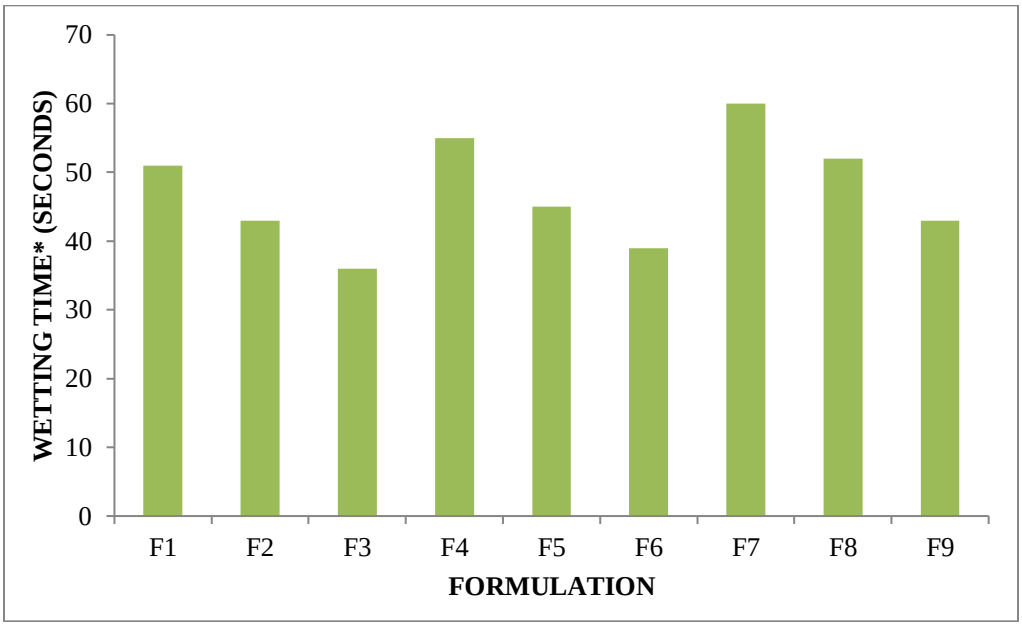

Figure 8.3 : Wetting time graph

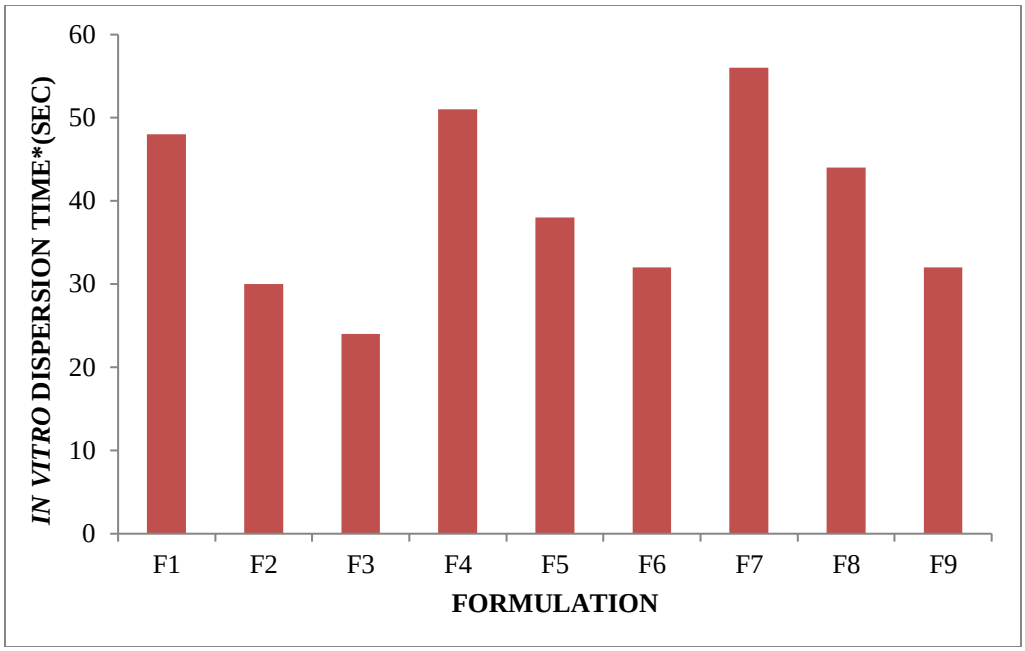

Figure 8.4 : *In vitro* dispersion time

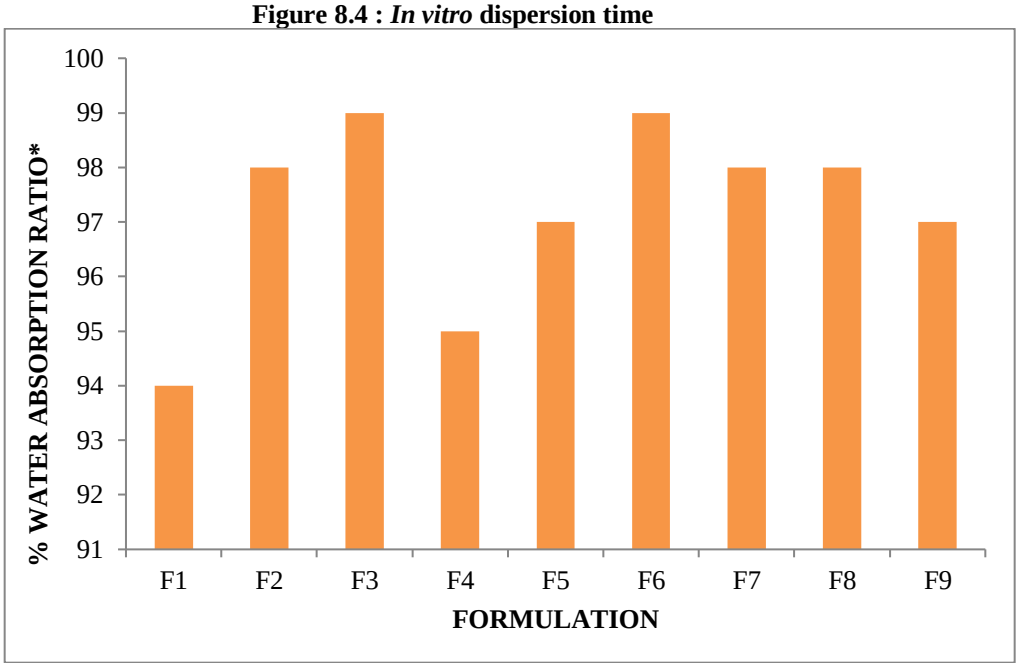

Figure 8.5 : Water absorption ratio graph

***In vitro* disintegration time:** *In vitro* disintegration studies showed from 28 to 48 secs. These results indicate that the F3 formulation which shown less disintegration time than remaining formulations.

Wetting time: Wetting time to the time required to wet completely when kept motionless on the tissue paper in a petridish.

- All the FDT formulations were evaluated for their wetting time as per the procedure described in the methodology section, and the results are shown in table.
- The average wetting time for all the formulations was in the range of **(36 to 60)** seconds.
- It was also observed that formula F3 which had the least wetting time also had the minimum disintegration time showing a strong correlation between disintegration time and wetting time.

***In vitro* dispersion time:** Lovastatin Mouth Dissolving Tablets F3 formulation dispersed time

was 24 secs. It was known that less dispersion time than other formulation.
The *In vitro* dispersion time for all formulation was found to be in a range of **24 to 56** seconds

Water Absorption ratio: All the formulations were evaluated for water absorption ratio according to the procedure described in methodology section and the results are shown in table.

- The maximum water absorption ratio was shown by formulation F3 showed 99 **%.**
- Water absorption ratio is proportional to dissolution rate profile as higher the water absorption ratio Higher the dissolution

***In vitro* drug release studies of Lovastatin**

Table 8.5: Dissolution data of Lovastatin

Time (Min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	34.15	45.93	52.87	41.56	50.92	56.25	29.93	46.92	52.54
10	47.93	58.20	61.38	65.24	65.01	67.42	38.65	57.16	62.30
15	58.71	65.14	76.11	73.98	83.36	78.71	61.57	75.34	68.17
20	74.24	81.96	87.96	81.47	90.28	85.98	76.19	84.25	89.25
30	84.31	92.83	99.72	89.34	95.17	96.03	87.21	90.17	97.51

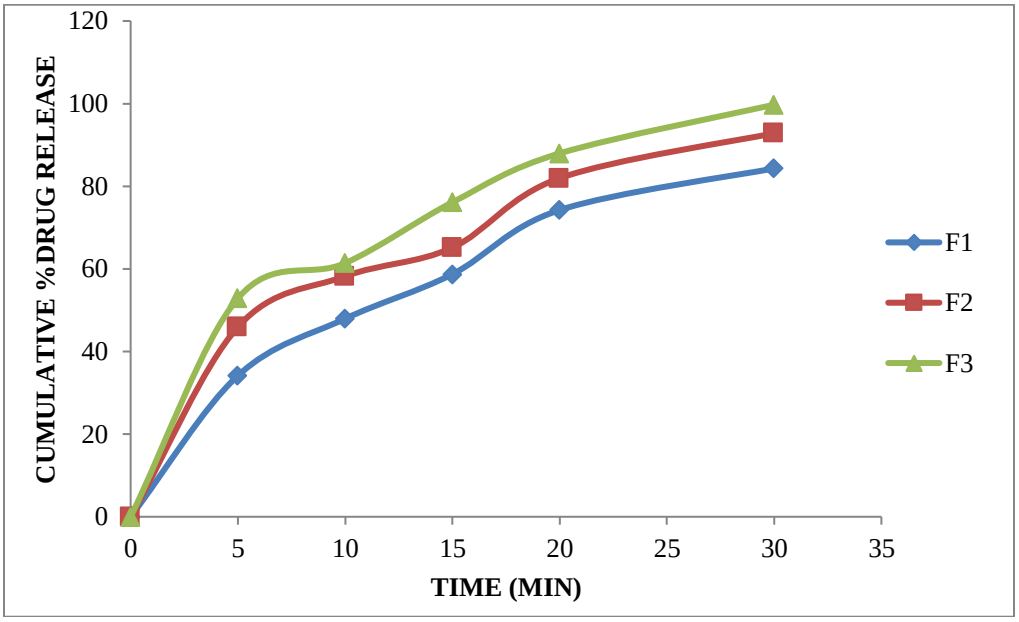

Fig 8.6 : Dissolution profile of formulations F1, F2, F3

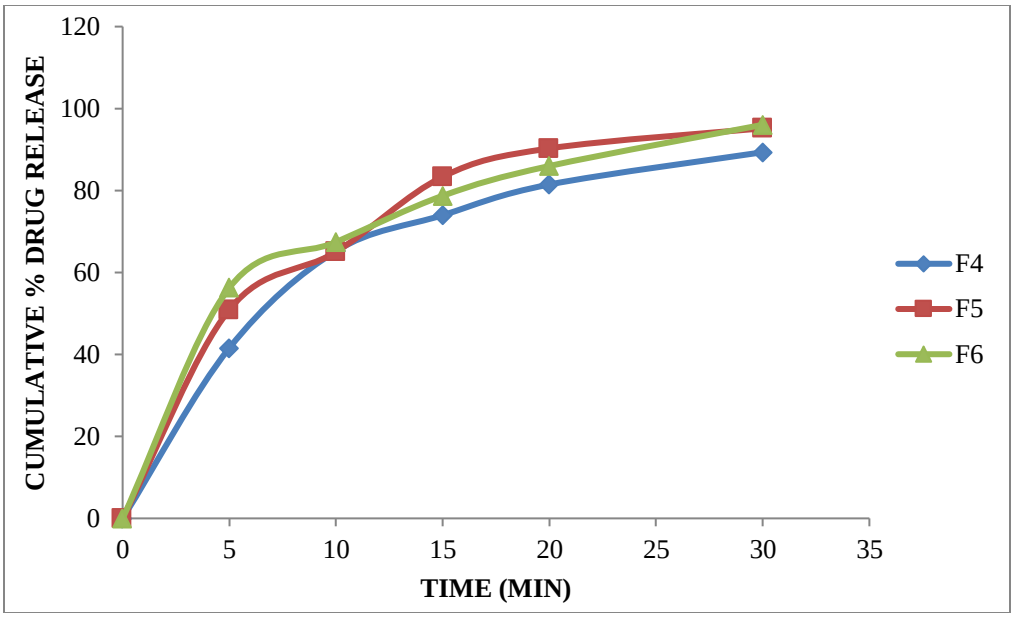

Fig 8.7 : Dissolution profile of formulations F4, F5, F6

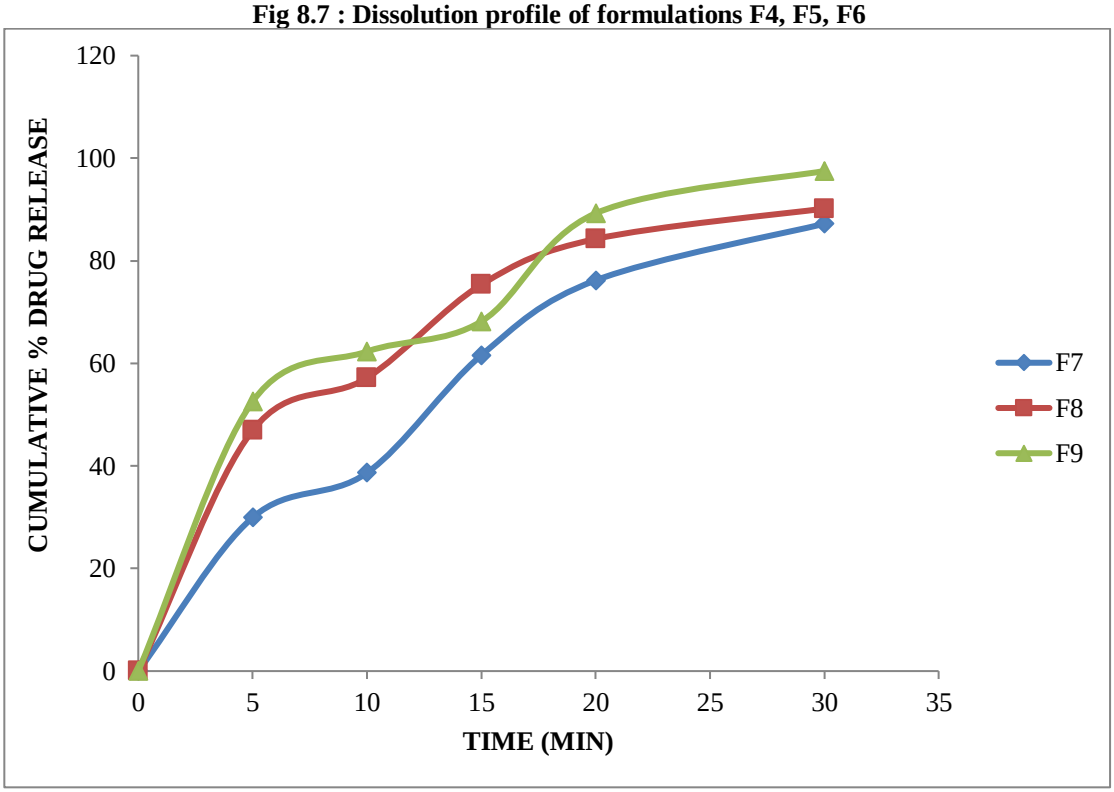

Fig 8.8 : Dissolution profile of formulations F7, F8, F9

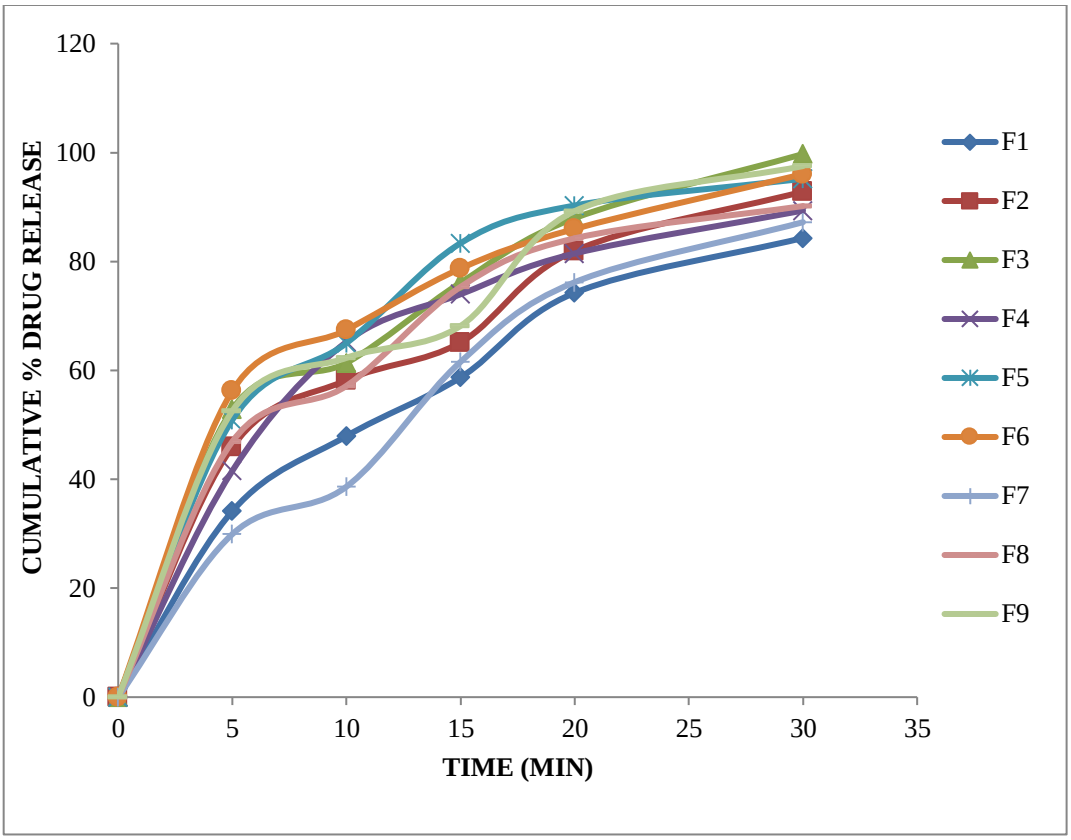

Fig 8.9 : Dissolution profile of all formulations F1-F9

The F3 formulation shows 99.72 % drug release in 30 min while using 75 mg concentration of Kyron T-314 and disintegration time is 28 sec. In which increase of concentration of Kyron T-314 improved dissolution and decreased disintegration so it was optimized formulation. Finally Concluded that F3 formulation was the optimized Formulation.

FTIR RESULTS:

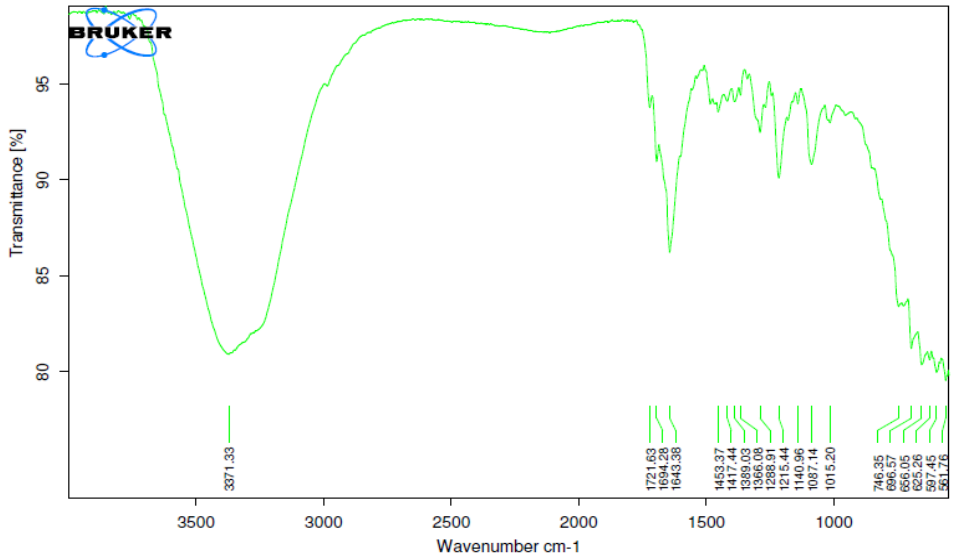

Fig 8.10: FTIR of Lovastatin Pure drug

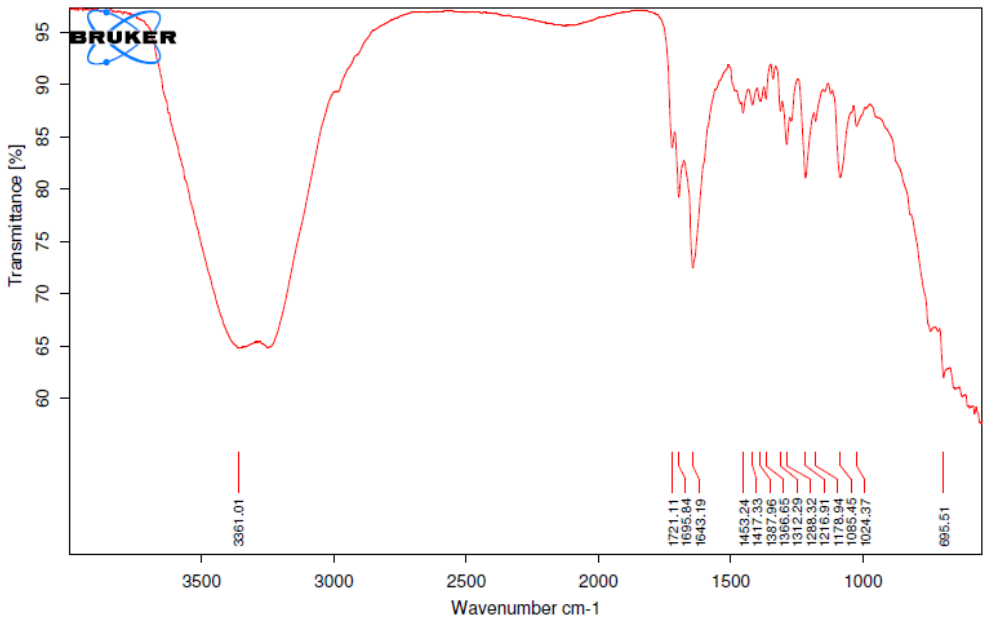

Fig 8.11: FTIR of Lovastatin optimized formulation

Lovastatin was mixed with proportions of excipients showed no colour change providing no drug-excipient interactions.

CONCLUSION:

It was concluded, that Lovastatin can be successfully formulated as mouth dissolving tablets using various superdisintegrants in different concentrations by direct compression method. The formulation containing 1:3 ratio of Kyron T-314 as superdisintegrant was found to be outstanding than other formulations in terms of disintegration time and rate of dissolution.

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