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Research

Development and Characterization of Linagliptin Oral Disintegrating Tablets

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Abstract

Linagliptin is an anti-diabetic drug used for the treatment of type 2 diabetes, it is belongs to the class of dpp-4 inhibitor. It has long half-life of about 8.6-23.9 hours and hence to achieve immediate therapeutic action it needs immediate release tablet formulation. Among the various techniques using superdisintegrants is a simple approach to formulate immediate release tablets. It undergoes an extensive hepatic first pass metabolism leads to low oral bioavailability (30%). ODT can overcome this problem through improving its bioavailability with an immediate drug release. In the present work, Oral disintegrating tablets of Linagliptin were prepared by direct compression method using superdisintegrants such as Crosspovidone lycoat, and Tulsion. The dispersion time of tablets were reduced with increase in the concentration of super disintegrants like Crosspovidone, lycoat, and Tulsion. From the results obtained, it was concluded that Tulsion was found to be the best among the superdisintegrants, the highest drug release of F9 is 99.45% of the drug in 20 min.

Keywords: Linagliptin, Crosspovidone, lycoat, Tulsion, Oral disintegrating tablets.

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.[1-2] 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 pediatric and geriatric patients[1] , but it also applies to people who are ill in bed and to those active working patients who are busy or traveling, especially those who have no access to water.[2] Over a decade, the demand for development of orally disintegrating tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. Orally disintegrating tablets are appreciated by a significant

segment of populations particularly who have difficulty in swallowing. It has been reported that Dysphagia[3] (difficulty in swallowing) is common among all age groups and more specific with pediatric, geriatric population along with institutionalized patients, psychiatric patients and patients with nausea, vomiting, and motion sickness complications.[1] ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population.

This dosage form combines the advantages of dry and liquid formulation. Some novel ODT technology allow high drug loading, have an acceptable taste, offer a pleasant mouth felling, leaving minimal residue in the mouth after oral administration. ODT have been investigated for their potential in improving bioavaibility of poorly soluble drug through enhancing the dissolution profile of the drug and hepatic metabolism drugs. Orally disintegrating tablets are also called as orodispersible tablets, quick disintegrating tablets, mouth dissolving tablets, fast disintegrating tablets, fast dissolving tablets, rapid dissolving tablets, porous tablets, and rapimelts. However, of all the above terms, United States pharmacopoeia (USP) approved these dosage forms as ODTs. Recently, European Pharmacopoeia has used the term orodispersible tablet for tablets that disperses readily and within 3 min in mouth before swallowing.[4] Some of super disintegrants employed in ODTs are discussed in Table 1. United States Food and Drug Administration (FDA) defined ODT as "A solid dosage form containing medicinal substance or active ingredient which disintegrates rapidly usually within a matter of seconds when placed upon the tongue." The disintegration time for ODTs generally ranges from several seconds to about a minute. [5]

Overview of Oral Mucosa

The anatomical and physiological properties of the oral mucosa have been extensively reviewed by several authors. The oral cavity comprises Journal of Applied Pharmaceutical Science 01 (04); 2011: 35-45 the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Fig. 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and the mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells (Fig. 2). The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss (Collins et al 1987). Beneath the epithelium are the basement membranes, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface of the mouth) and the gingival (gums) (Smart et al, 2004). The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity.

Preformulation studies

It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies.

Determination of Melting Point

Melting point of Linagliptin was determined by capillary method. Fine powder of Linagliptin was filled in glass capillary tube (previously sealed at one end). The capillary tube was tied to thermo meter and the thermometer was placed in the Thais tube and this tube was placed on fire. The powder at what temperature it melted was noticed.

Solubility

Solubility of Linagliptin was determined in pH 1.2, pH 6.8 and pH 7.4 phosphate buffers. Solubility studies were performed by taking excess amount of Linagliptin in different beakers containing the solvents. The mixtures were shaken for 24hrs at regular intervals. The solutions were filtered by using whattmann's filter paper grade 41. The filtered solutions were analyzed spectrophotometrically at 236 nm.

Compatibility Studies

FTIR analysis

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2% (w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of $2cm^{-1}$ using Happ-Genzel apodization. The characteristic peaks were recorded.

Calibration curve for linagliptin in distilled water

Procedure

Preparation of Standard Stock Solution

10 mg of Linagliptin was accurately weighed into 10 ml volumetric flask and volume was made up to 10 ml with the 6.8pP buffer to get a concentration of (1000 µg/ml) SS-I. From this, 1 ml was withdrawn and diluted to 100 ml with 6.8pP buffer to get a concentration of (100 µg/ml) SS-II.

Scanning of Drug

From stock solution (SS-II), 1 ml was withdrawn and the volume was made up to 10 ml with 6.8pP buffer to get a concentration of 10 µg/ml. UV scan range was taken between the wavelengths 200-400 nm. It gave a peak at 230 nm and the same was selected as λ_{max} for Linagliptin.

Calibration Curve in distilled water

From the standard stock solution (SS-II), 0.2,0.4,0.6,0.8,1.0, and 1.2 ml were withdrawn and volume was made up to 10 ml with 6.8pH buffer to give a concentration of 2,4,6,8,10,and 12µg/ml. Absorbance of these solutions was measured against a blank of 6.8pP buffer at 230 nm for Linagliptin and the absorbance values are summarized in results section. Calibration curve was plotted, drug concentrations versus absorbance was given in the Fig in results section.

Disintegrants and mechanism of action

A disintegrant is an excipient, which is added to aid in the breakup of the compacted mass, when put into a fluid environment. This is especially important for immediate release product where rapid release of product is required.

The proposed mechanisms of action of disintegrants include:

1. Water uptake through wicking
2. Swelling
3. Deformation (shape recovery)
4. Particle repulsion
5. Heat of wetting

The later two mechanisms are not well supported by research.

Water penetration is an indispensable preprocessing step for disintegration. The sorption properties of various disintegrants are found to be essential for efficient disintegration and dissolution. If the wetting of the superdisintegrants is slow, for example by coating the disintegrant with a hydrophobic substance, disintegration of the mass is also slowed. The extensive research on superdisintegrants has not only implicated the extent of water uptake is important but also have conclusively demonstrated that the rate of water uptake is of critical importance for number of disintegrants.

Drug-Excipient Compatibility Studies By I.R

Excipients are integral components of almost all pharmaceutical dosage forms. The successful formulation of a stable and effective solid dosage form depends on the careful selection of the excipients, which are added to facilitate administration, promote the consistent release and bioavailability of the drug and protect it from degradation.

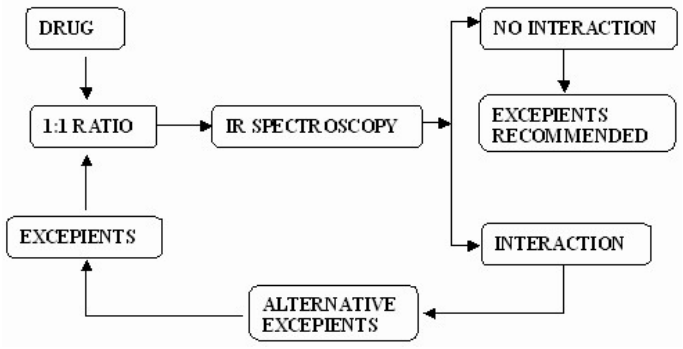

Fig 1: Schematic representation of compatibility studies

Infra Red spectroscopy is one of the most powerful analytical techniques to identify functional groups of a drug.

Method

The pure drug and its formulation were subjected to IR studies. In the present study, the potassium bromide disc (pellet) method was employed.

The drug-polymer interactions were studied by FTIR spectrometer, Shimadzu 8400 S. 2%(w/w) of the sample, with respect to a potassium bromide (KBr; SD Fine Chem. Ltd., Mumbai, India) was mixed with dry KBr. The mixture was ground into a fine powder using mortar and then compressed into a KBr discs in a hydraulic press at a pressure of 10000 PSI. Each KBr disc was scanned 10 times at a resolution of $2cm^{-1}$ using Happ-Genzel apodization. The characteristic peaks were recorded.

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Formulation of oral disintegrating tablets of linagliptin [29]

Oral disintegrating tablets of Linagliptin were prepared by direct compression according to the formulae given in the table 1.

All the ingredients were passed through #60 mesh sieve separately. The drug and micro crystalline cellulose (MCC) were mixed by adding small portion of each at a time and blending it to get a uniform mixture and kept aside.

Then the other ingredients were mixed in geometrical order and passed through coarse sieve (#44 mesh) and the tablets were compressed using hydraulic press. Compression force of the machine was adjusted to obtain the hardness in the range of 3-4 kg/cm^2 for all batches. The weight of the tablets was kept constant for all formulations F1to F9 (150 mg).

Table 1: Oral Disintegrating Tablets Of Linagliptin

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Linagliptin	5	5	5	5	5	5	5	5	5
Ludiflash	5	7.5	10	-	-	-	-	-	-
Lycoat	-	-	-	5	7.5	10	-	-	-
Tulsion	-	-	-	-	-	-	5	7.5	10
Aspartame	12	12	12	12	12	12	12	12	12
Mannitol	30	30	30	30	30	30	30	30	30
M.C.C	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.	Q.S.
Magnesium stearate	6	6	6	6	6	6	6	6	6
Talc	6	6	6	6	6	6	6	6	6
Total weight (mg)	150	150	150	150	150	150	150	150	150

RESULTS & DISCUSSION

In the present study, an attempt has been made to formulate and evaluate Oral disintegrating tablets of Linagliptin by direct compression method using Tulsion, Ludiflash, Lycoat as superdisintegrants. Nine formulations were prepared and complete composition of all batches shown in Table 3. The tablets were then characterized for various physico-chemical parameters.

Preformulation studies

Determination of melting point

The melting point of Linagliptin was found to be 194° C which was determined by capillary method.

Solubility

Solubility of Linagliptin was carried out at 25^0C using 0.1 N HCL, 6.8 phosphate buffer, and purified water.

Table 2: Solubility of Linagliptin

S.NO	MEDIUM	SOLUBILITY(mg/ml)
1	Water	0.156
2	0.1 N HCL	0.205
3	6.8 PH buffer	0.384

4	7.4pH buffer	0.328

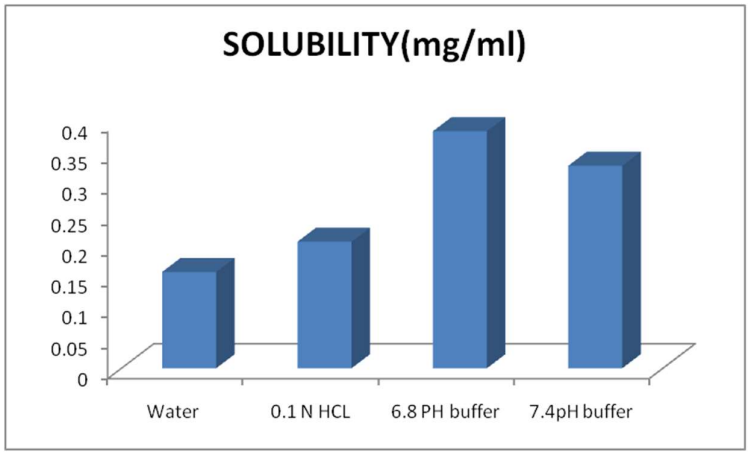

Fig 2: Solubility studies of Linagliptin

From the above conducted solubility studies in various buffers we can say that 6.8pH buffer solution has more solubility when compared to other buffer solutions.

Standard Calibration Curve Of Linagliptin IN 6.8pH buffer

Standard calibration curve of Linagliptin was drawn by plotting absorbance v/s concentration. The λmax of Linagliptin in 6.8pH buffer was determined to be 236 nm as shown in Fig. 2. The absorbance values are tabulated in Table 4. Standard calibration curve of Linagliptinin the Beer's range between 0-12µg/ml is shown in Fig.3.

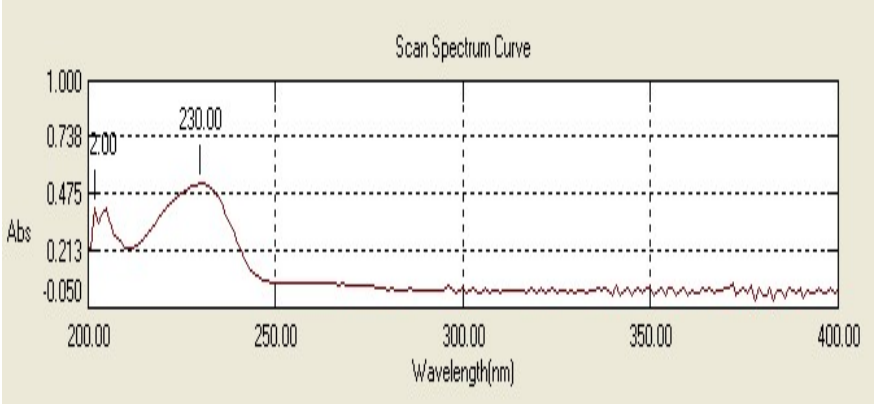

Fig 3: Calibration Curve Of Linagliptin IN 6.8pH buffer

Table 3: Calibration data of Linagliptin in 6.8pH buffer at λ_{max} 230 nm

SL. No.	Concentration (µg/ml)	Absorbance*
1	0	0
2	2	0.196
3	4	0.364
4	6	0.519
5	8	0.691
6	10	0.876
7	12	1.036

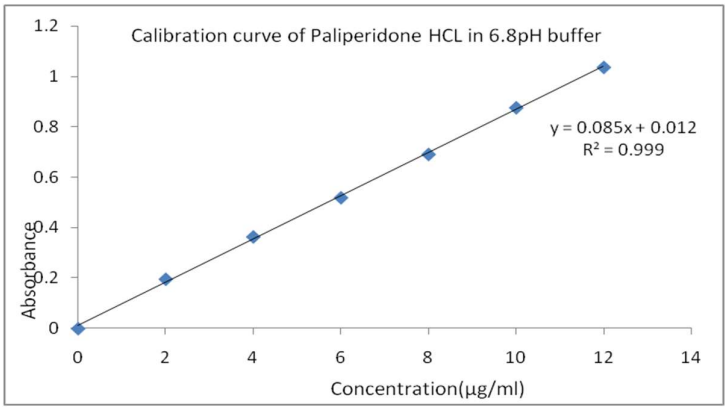

Fig 4: Standard calibration curve for Linagliptin in 6.8pH buffer at λmax 230 nm.

Compatibility Study

Compatibility studies were performed using FT-IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied by making a KBr disc. The characteristic absorption peaks of Linagliptin were obtained at different wave numbers in different samples.The peaks obtained in the spectra of each formulation correlates with the peaks of drug spectrum. This indicates that the drug is compatible with the formulation components.

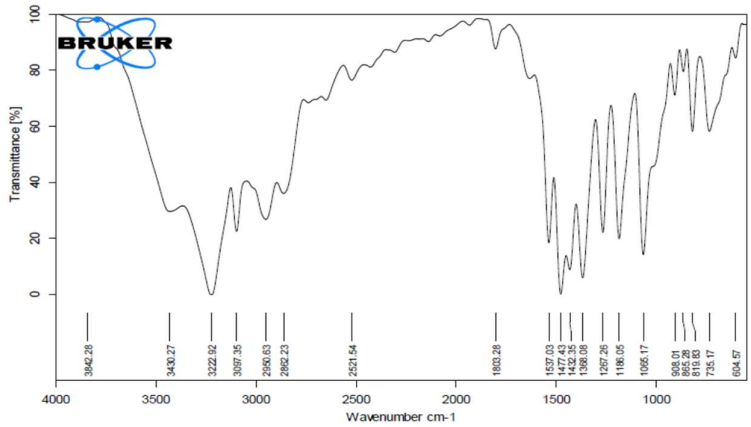

Fig 5: Ftir Graph of Linagliptin

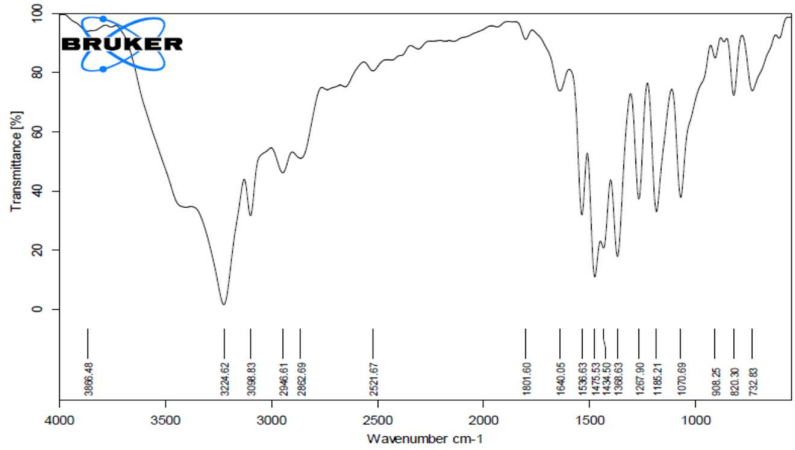

Fig 6: Ftir Graph Of Optimized Formulation

From the drug and excipients interaction studies it was identified that the pure drug and the optimized formulation have no interactions when compared with the pure drug functional groups.

Table 4: Pre Compression parameters

Formulation Code	Derived properties		Flow properties		
	Tapped density (mean±SD)	Bulk density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.48±0.01	0.56±0.015	26.38±0.30	14.28±1.02	1.16±0.06
F2	0.46±0.01	0.52±0.02	27.42±0.39	11.53±1.26	1.13±0.03
F3	0.42±0.04	0.48±0.01	24.02±0.68	12.58±2.08	1.14±0.05
F4	0.46±0.02	0.54±0.015	26.26±0.96	14.81±1.28	1.12±0.02
F5	0.52±0.6	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F6	0.49±0.2	0.58±0.006	29.26±0.36	15.51±1.96	1.18±0.05
F7	0.42±0.08	0.48±0.04	24.02±0.68	12.58±2.08	1.14±0.05
F8	0.52±0.12	0.60±0.03	30.68±0.73	13.33±1.86	1.17±0.04
F9	0.42±0.06	0.48±0.01	24.02±0.52	12.58±1.08	1.14±1.05

The angle of repose of different formulations was ≤ 30.68 which indicates that material had good flow property. So it was confirmed that the flow property of blends were free flowing. The bulk density of blend was found between 0.42g/cm^3 to 0.52g/cm^3.Tapped density was found between 0.48g/cm^3 to 0.60g/cm^3.These values indicate that the blends had good flow property. Carr's index for all the formulations was found to be between 11.53-15.518 and Hausner's ratio from 1.12-1.18 which reveals that the blends have good flow character.

Table 5: Post compression parameters

Formula	Post compression parameters					
	Avg.Wt (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)	Disintegration time(secs)	Drug content (%)
F1	149.2±0.02	3.34±0.76	3.41±0.26	0.23±0.46	86±0.01	87.95±0.54
F2	151.9±0.23	3.12±0.55	3.69±0.03	0.41±0.08	63±0.56	90.55±0.65
F3	150.6±0.56	3.30±0.29	3.97±0.05	0.77±0.04	47±0.36	93.4±0.247
F4	150.2±0.03	3.20±0.15	3.55±0.16	0.54±0.01	79±0.54	96.7±0.344
F5	99.2±0.01	3.33±0.09	3.36±0.17	0.63±0.55	58±0.26	82.9±0.493
F6	148.8±0.10	3.45±0.08	3.64±0.65	0.70±0.46	39±0.35	89.52±0.16
F7	151.9±0.25	3.36±0.03	3.40±0.53	0.19±0.56	71±0.01	93.6±0.42
F8	152.5±0.29	3.55±0.46	3.39±0.15	0.35±0.21	53±0.02	98.34±0.5
F9	148.4±0.75	4.02±0.25	3.77±0.42	0.48±0.32	30±0.56	99.89±0.16

Weight Variation Test

The percentage weight variations for all formulations were given. All the formulated (F1 to F9) tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits. The weights of all the tablets were found to be uniform with low standard deviation values.

Hardness test

The measured hardness of tablets of all the formulations ranged between 3-4 kg/cm2. This ensures good handling characteristics of all batches.

Disintegration test for core tablets

It was found between 30 – 86 seconds ensuring that all the cores of different formulations were rapid disintegrating type.

Friability Test

The % friability was less than 1 % in all the formulations ensuring that the tablets were mechanically stable.

SUMMARY & CONCLUSION

Linagliptin is an anti-diabetic drug used for the treatment of type 2 diabetes, it is belongs to the class of dpp-4 inhibitor. It has long half-life of about 8.6-23.9 hours and hence to achieve immediate therapeutic action it needs immediate release tablet formulation. Among the various techniques using superdisintegrants is a simple approach to formulate immediate release tablets. It undergoes an extensive hepatic first pass metabolism leads to low oral bioavailability (30%). ODT can overcome this problem through improving its bioavailability with an immediate drug release.

In the present work, Oral disintegrating tablets of Linagliptin were prepared by direct compression method using superdisintegrants such as Ludiflash lycoat, and Tulsion. From the results obtained, it can be concluded that:

- The flow properties of polymer and drug were good.
- FT-IR studies revealed that there is no chemical interaction between Linagliptin and the excipients used in the study.
- The tablets prepared were found to be good without any chipping, capping and sticking.
- Formulated tablets gives satisfactory result for various physico-chemical evaluation of tablets like tablet dimension, hardness, friability, weight variation, *in vitro* dispersion time, and drug content.
- The low values of standard deviation for average weight and drug content of the prepared tablets indicate weight and drug content uniformity within the batches prepared.
- The in-vitro dissolution study of Linagliptin tablet is tested in phosphate buffer 6.8(simulated fluid) From the *in vitro* dissolution data, it was found that the drug release study from formulations containing Ludiflash as super disintegrant (F_1-F_3). F1 formulation shows maximum drug release at the end of 95.5% at the end of 30mins. Whereas F2 formulation shows maximum drug release at the end of 98.07% at the end of 30mins, while F3 formulation shows maximum drug release at the end of 97.4% at the end of 25mins.

While the Formulations containing lycoat as super disintegrant (F_4-F_6) showed 92.7, 97.19, 96.66% of drug release respectively at the end of 30, 25 and 20 mins respectively. Whereas the Formulations containing Tulsion as super disintegrant (F_7-F_9) showed 99.78, 98.91, 99.45% of drug release respectively at the end of 30, 25 and 20mins. From the in vitro dissolution studies it was observed that the increase in the super disintegrant concentration proportionally decreases the time taken for the dissolution. It was observed from the results that, formulations containing Tulsion as super disintegrant showed maximum dissolution rate 99.45% of drug release in F9 in 20 min. This shows that effectiveness of superdisintegrants are in the order of Tulsion> Lycoat > Ludiflash. The concentration of superdisintegrants in the formulations also increased the dissolution rates. It was observed from the results that, formulations containing Tulsion as super disintegrant showed maximum dissolution rate 99.45% of drug release in F9 in 20 min.

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