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FORMULATION AND EVALUATION OF ORAL DISINTEGRATING TABLETS OF URAPIDIL

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ABSTRACT

The aim of present study was to develop the Urapidil oral disintegrating tablets thereby enhancing the solubility and dissolution rate. Dissolution rate was enhanced by using various disintegrants like Ocimum mucilage, Locust bean gum, Sodium Starch Glycolate, β-cyclodextrin, poloxamer 407 and it was further confirmed by phase solubility studies. The formulated tablets were evaluated and the parameters such as weight variation, hardness, friability, drug content, thickness, disintegration and dissolution studies were compiled with the official limits. From the in-vitro dissolution studies, it was observed that the formulation F6 consists of Locust bean gum showed maximum drug release (99.96%) in 25 minutes. FTIR data also reveals that there is no chemical interaction between drug and excipients in the present investigation.

KEYWORDS: Urapidil, oral disintegrating tablets, locust bean gum, dissolution rate.

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 pediatric and geriatric patients. 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. 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. (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. 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.

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]

Drug selection criteria

The ideal characteristics of a drug for oral dispersible tablet include

- Ability to permeate the oral mucosa.
- At least partially non-ionized at the oral cavity pH.
- Have the ability to diffuse and partition into the epithelium of the upper GIT.
- Small to moderate molecular weight.
- Low dose drugs preferably less than 50 mg.
- Short half-life and frequent dosing drugs are unsuitable for ODT.
- Drug should have good stability in saliva and water.
- Very bitter or unacceptable taste and odor drugs are unsuitable for ODT[6]

Desired criteria for ODTs

- ODT should leave minimal or no residue in mouth after oral administration, compatible with pleasing mouth feel.
- Effective taste masking technologies should be adopted for bitter taste drugs.
- Exhibit low sensitivity to environment condition such as humidity and temperature.
- ODTs should dissolve / disintegrate in the mouth in matter of seconds without water.
- Have sufficient mechanical strength and good package design.
- The drug and excipients property should not affect the orally disintegrating tablets.
- Be portable and without fragility concern.[7,8]

Advantages of ODTs

The advantages of ODTs include:

No need of water to swallow the tablet.

- Compatible with taste masking and have a pleasing mouth feels.
- Can be easily administered to pediatric, elderly and mentally disabled patients.
- No residue in the oral cavity after administration.
- Manufacturing of the tablets can be done using conventional processing and packaging equipment's at minimum cost. Allow high drug loading.
- Accurate dose can be given as compared to liquids.
- Dissolution and absorption of the drug is fast, offering a rapid onset of action.
- Advantageous over liquid medication in terms of administration as well as transportation. Some amount of drugs is absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach, thus reducing first pass metabolism, which offers improved bioavailability and thus reduced dose and side effects.
- No risk of suffocation due to physical obstruction when swallowed, thus offering improved safety.
- ODTs are suitable for sustained and controlled release actives.
- Unit packaging.[9,10]

Disadvantages of ODTs

- ODT is hygroscopic in nature so must be keep in dry place
- Some time it possesses mouth feeling.
- It is also shows the fragile, effervescence granules property
- ODT requires special packaging for properly stabilization & safety of stable product

Limitations of ODTs

It includes

- The tablets commonly have insufficient mechanical strength. Hence, conscientious handling is necessary.
- The tablets may leave an unpalatable taste and grittiness in the oral cavity if not formulated properly.
- Drugs which have large doses can cause problems to formulate them into ODTs.
- Patients who simultaneously take ant cholinergic drugs are not suitable candidates for ODTs.

Approaches for Preparation of Odts

Various preparation techniques have been developed on the basis of different principles, thus present different properties of ODTs by means of mechanical strength, stability, mouth feel, and taste, swallow ability, dissolution profile and bioavailability. Some of those technologies are patented. Basic pharmaceutical processes to manufacture ODTs are explained as follows:

Spray drying

Sublimation

Freeze drying

Molding

Mass extrusion

Direct compression

Ideal characteristics of ODTs

ODTs should depict some ideal characteristics to distinguish them from traditional conventional dosage forms. Important desirable characteristics of these dosage forms include

1. No water requirement for swallowing purpose but it should dissolve or disintegrate in the mouth usually within fraction of seconds.
2. Provide pleasant feeling in the mouth.
   3. be compatible with taste masking.
3. Be portable without fragility concern.
4. Leave negligible or no residue in the mouth after oral administration.
5. Exhibit low sensitivity to altered environmental conditions such as humidity and temperature.
6. Allow high drug loading.

7. Adaptable and amenable to conventional processing and packaging equipment at nominal expense.

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 v0.2 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 Urapidil

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 238nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Urapidil 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 1.0 ml, 2.0 ml, 3.0 ml, 4.0 ml, 5.0 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 10,20,30,40 and 50µg/ml respectively. The absorbance of each concentration was measured at respective (λ max) i.e., 238nm.

Formulation development

Drug and different concentrations of super disintegrates (Ocimum mucilage, Locust bean gum, Sodium starch glycolate.) 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.

Formulation table showing various compositions

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Urapidil	25	25	25	25	25	25	25	25	25
Ocimum mucilage	4	8	12	-	-	-	-	-	-
Locust bean gum	-	-	-	4	8	12	-	-	-
SSG	-	-	-	-	-	-	4	8	12
b cyclodextrin	6	6	6	6	6	6	6	6	6
poloxamer 407	6	6	6	6	6	6	6	6	6
Talc	3	3	3	3	3	3	3	3	3
Magnesium stearate	3	3	3	3	3	3	3	3	3
MCC	73	69	65	73	69	65	73	69	65
Total weight	120	120	120	120	120	120	120	120	120

(All the quantities are mentioned in mg only.)

The tablets were prepared by using tablet compression machine. The hardness of the tablet was maintained as (1.76±0.95 to 2.65±0.66) kg/cm^2

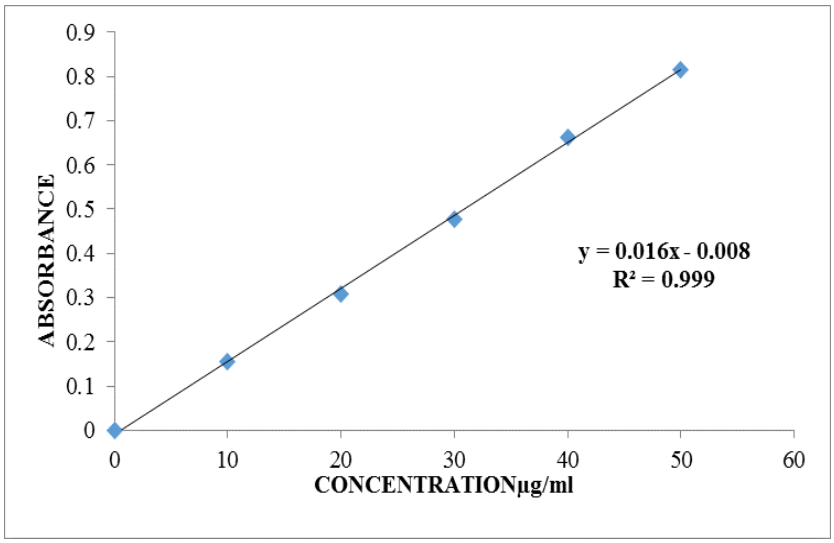
RESULTS AND DISCUSSION

Preparation of calibration curve of Urapidil

The regression coefficient was found to be 0.999 which indicates a linearity with an equation of y = 0.016x - 0.008 Hence Beer-Lambert's law was obeyed.

Calibration curve data of Urapidil in pH 6.8 phosphate buffer.

Concentration	Absorbance
0	0
10	0.156
20	0.309
30	0.476
40	0.662
50	0.816



Calibration curve of Urapidil

EVALUATION OF PRE-COMPRESION PARAMETERS OF POWDER BLEND

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	30.12±0.03	0.429±0.02	0.520±0.02	17.50	1.21
F2	28.78±0.03	0.426±0.01	0.521±0.02	18.23	1.22
F3	32.08±0.02	0.412±0.03	0.508±0.05	18.90	1.23
F4	31.06±0.04	0.431±0.04	0.519±0.04	16.96	1.20
F5	29.67±0.01	0.439±0.04	0.537±0.04	18.24	1.22
F6	28.45±0.02	0.429±0.04	0.518±0.05	17.18	1.20
F7	32.08±0.01	0.439±0.03	0.515±0.02	14.75	1.17
F8	31.06±0.01	0.423±0.03	0.529±0.05	20.03	1.25
F9	29.67±0.02	0.436±0.04	0.536±0.04	18.65	1.23

- 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 0.412±0.03 to 0.439±0.04 and tapped density was in the range of 0.508±0.05 to 0.536±0.04
- The Carr's index and Hausner's ratio was calculated from tapped density and bulk density.

EVALUATIONS OF POST COMPRESSION PARAMETERS OF URAPIDIL ODTs

Evaluation of post compression parameters of Urapidil Fast dissolving tablets

Formulation codes	Average weight(mg)	Hardness (kg/cm^2	Friability (%loss)	Thickness (mm)	Drug content (%)	In vitro disintegration Time(min)
F1	119	2.15±0.12	0.26±0.35	1.16±0.27	99.34	15
F2	121	2.58±0.27	0.34±0.48	1.23±0.69	98.96	18
F3	118	2.65±0.66	0.55±0.96	1.29±0.45	97.22	16
F4	119	2.12±0.24	0.43±0.76	1.47±0.21	99.37	16
F5	120	2.27±0.38	0.39±0.54	1.35±0.68	99.68	12
F6	122	1.89±0.63	0.47±0.22	2.12±0.75	98.76	8
F7	117	1.96±0.41	0.29±0.52	1.85±0.37	97.65	19
F8	118	1.76±0.95	0.38±0.39	1.66±0.95	99.49	22
F9	120	2.23±0.72	0.42±0.14	1.57±0.62	98.29	23

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 ODT 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 (1.76±0.95 to 2.65±0.66) 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 transporting. All the ODT 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 0.26±0.35 to 0.55±0.96 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 (97 -99.). 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 ODT formulation complies with the standards given in IP.

***In vitro* Dissolution time:** *In vitro* disintegration studies showed from 8-23 minutes. The F6 formulation showed in vitro dissolution time i.e. 25 minutes.

IN VITRO DRUG RELEASE SYUDIES OF URAPIDIL

Dissolution data of Urapidil

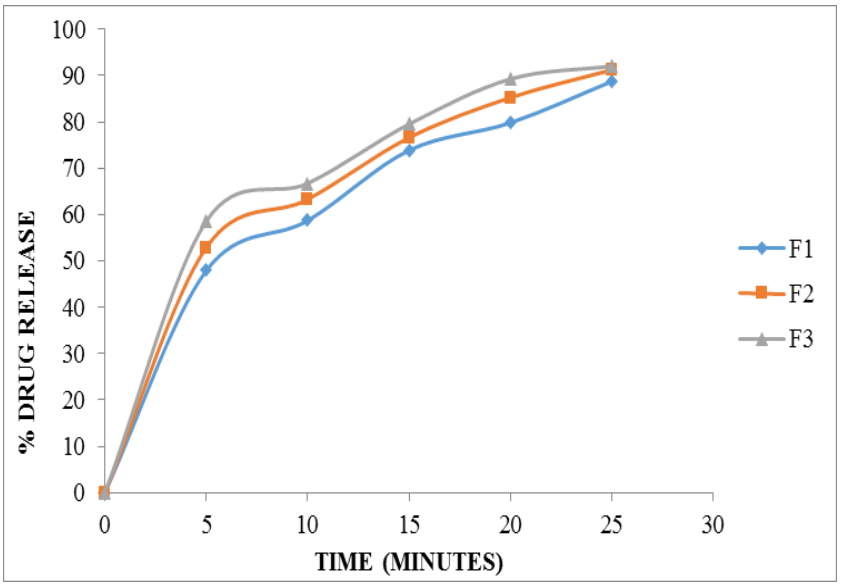
TIME(MIN)	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0	0	0	0	0	0	0	0	0
5	47.93	52.86	58.58	56.81	62.11	65.69	55.46	53.59	65.71
10	58.74	63.23	66.72	69.44	75.01	77.65	61.28	66.12	76.97
15	73.89	76.52	79.51	73.73	83.75	86.38	78.58	79.74	85.92
20	79.83	85.15	89.23	85.13	88.06	93.82	86.06	87.33	89.45
25	88.74	91.11	92.02	93.72	96.58	99.96	93.51	95.54	94.12

Among all the formulations F6 was showed good drug release

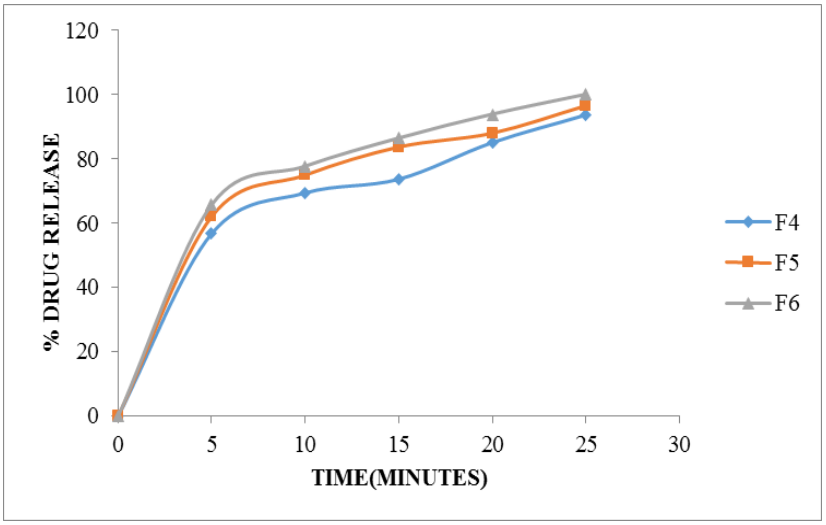
Formulation	Average weight(mg)	Hardness (kg/cm^2	Friability (%loss)	Thickness (mm)	Drug content (%)	In vitro disintegration Time(min)
F6	122	1.89±0.63	0.47±0.22	2.12±0.75	98.76	8

F6 Optimized Formulation Dissolution Profile.

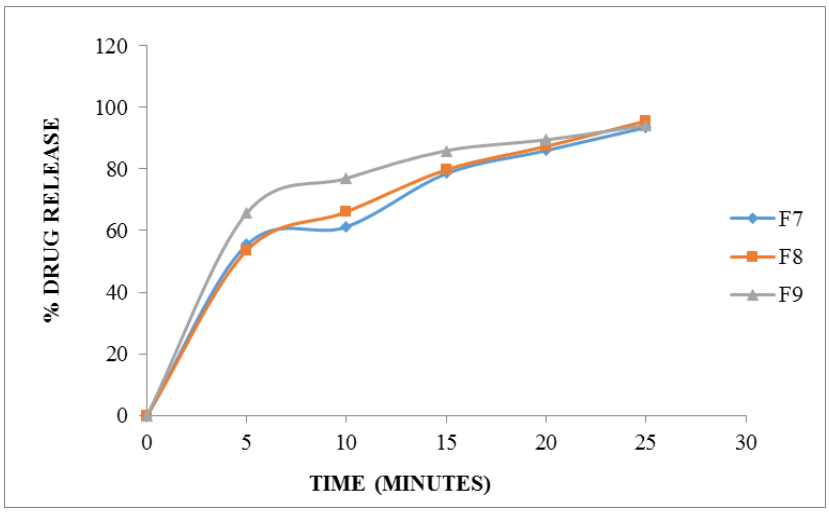
Time (minutes)	F6
0	0
5	65.69
10	77.65
15	86.38
20	93.82
25	99.96



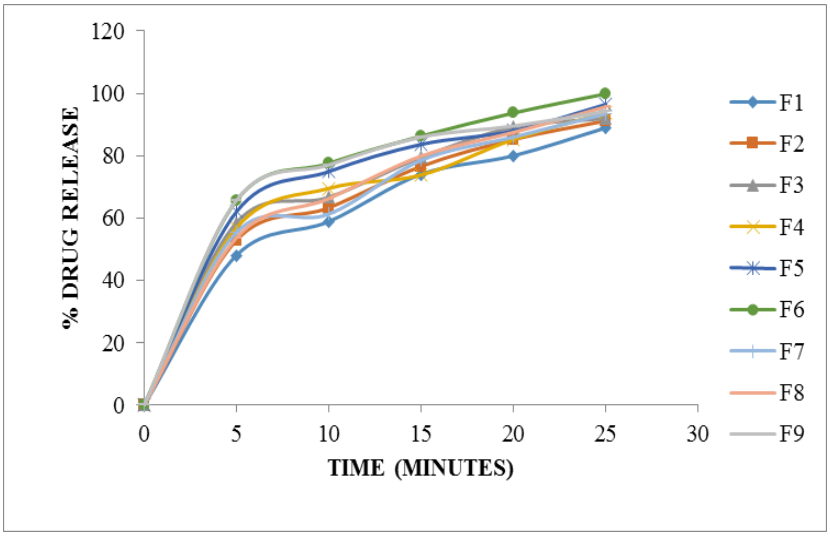
Dissolution profile of formulations F1, F2, F3



Dissolution profile of formulations F4, F5, F6

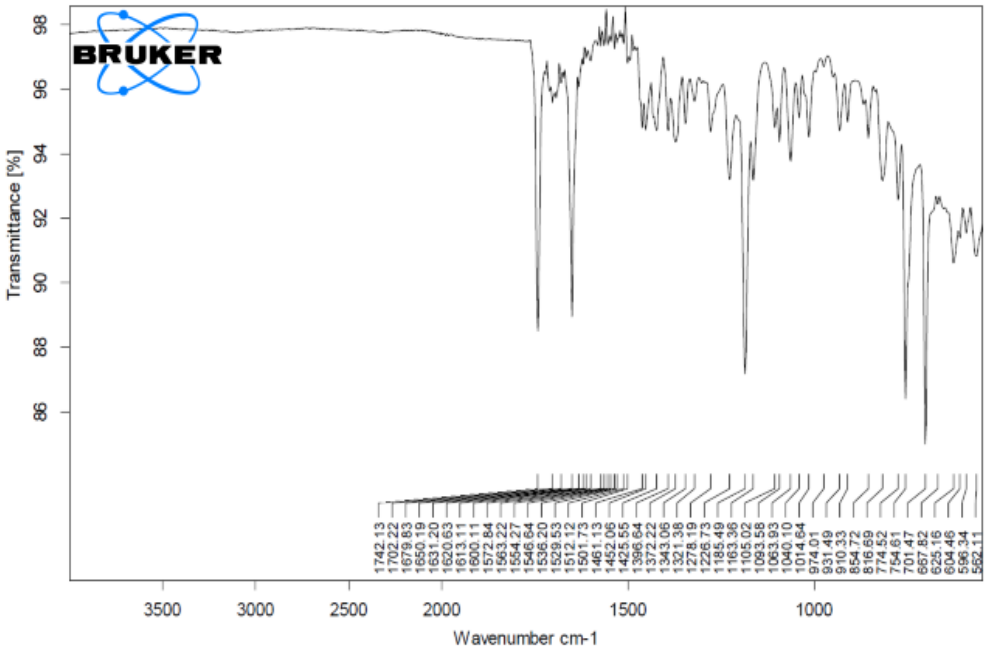


Dissolution profile of formulations F7, F8, F9

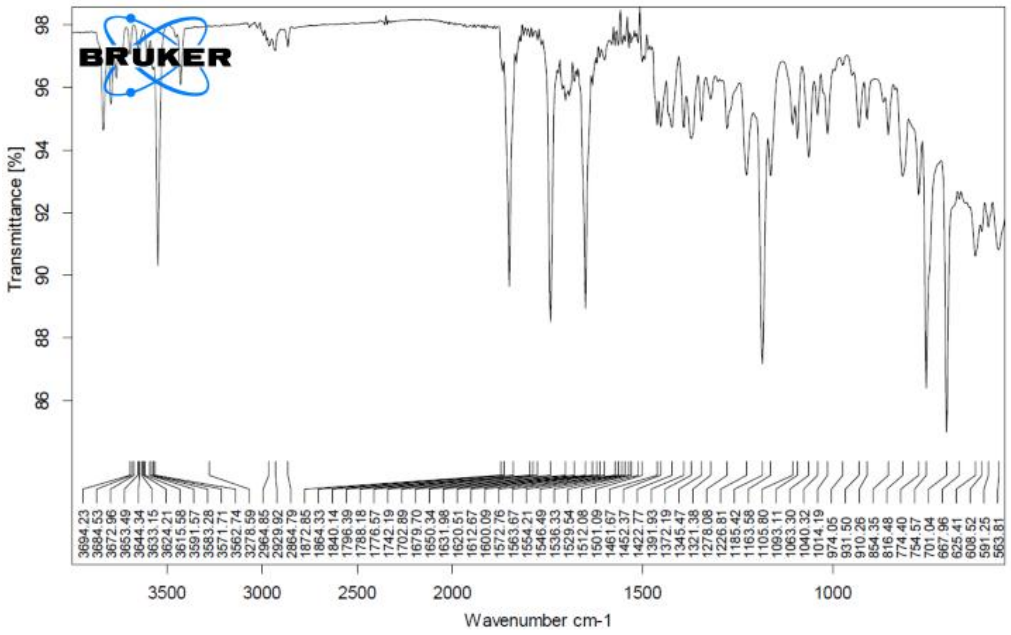


Dissolution profile of all formulations F1-F9

FTIR RESULTS



FTIR of Urapidil Pure Drug



FTIR of Urapidil optimized formulation

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

CONCLUSION

The overall results indicate that formulation with Locust bean gum had higher edge compared to other formulations. The formulation containing the polymer locust bean gum satisfy all the

criteria for oral disintegrating tablet of Urapidil compared to formulations containing Ocimum mucilage & sodium starch glycolate. This direct compression process is simple, reproducible and robust to prepare orally disintegrating tablets of Urapidil.

Among all the formulations, F6 formulation (12 mg of Locust bean gum) showed the maximum percentage drug release i.e., 99.96% in 25 minutes and the other evaluation parameters like weight variation test shown average weight of 122mg, hardness (1.89±0.63 kg/cm^2), friability (0.47±0.22% loss), thickness (2.12±0.75 mm), drug content (98.76%), and invitro disintegration time (8 min). Hence F6 was considered as an optimized formulation for the preparation of Urapidil oral disintegrating tablet formulation delivery system.

The above results also suggest that the formulated oral disintegrating tablets of Urapidil exhibited good physical parameters and rapidly disintegrating without affecting the release profile and is very effective in case of elderly and pediatric patients.

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