Journal of Pharma Creations (JPC)

JPC |Vol.11 | Issue 4 | Oct - Dec -2024

www.pharmacreations.com

DOI : https://doi.org/10.61096/jpc.v11.iss4.2024.378-385

ISSN: 2348-6295

Research

Formulation And Evaluation Of Haloperidol Fast Dissolving Tablets

Kadimi Devi Sravani*[1], B. Deekshi Gladiola[1], Buddha Sravana Sree[1]

[1]*Department of Pharmaceutics, Pydah College of Pharmacy Patavala, Andhra University, Kakinada, Andhra Pradesh, India*

*Author for Correspondence: Kadimi Devi Sravani
Email: sravanidevi12345@gmail.com

Published on: 24 Nov 2024

Published by:
DrSriram Publications

Abstract

The demand for fast dissolving tablets has been growing during the last decade . especially for elderly children who have swallowing difficulties. In the present work fast dissolving tablets of Haloperidol were prepared Sodium croscarmellose, Crospovidone and Sodium starch glycolate as super disintegrants by the direct compression method. The tablets prepared were evaluated for various parameters including weight variation, hardness, friability, in vitro drug release and drug content are within the limits as per IP limits. Fats dissolving tablets of Haloperidol have enhanced dissolution and will lead to improved bioavailability and more effective therapy.

Keywords: Haloperidol, Sodium croscarmellose, Crospovidone and Sodium starch glycolate.

INTRODUCTION

The Fast 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 Fast 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 Fast cavity have attracted a great deal of attention. Fast dispersible tablets are not only indicated for people who have swallowing difficulties, but also are ideal for active people.[1]

An Fast disintegrating tablet (FDT) 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 FDT 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 ‘Fastdispersible tablet’ as a tablet that is to be placed in the Fast where it disperses

rapidly before swallowing. Fastly disintegrating tablets are also called as Fast-dissolving tablets, fast disintegrating tablets, fast dissolving tablets, Fastdispersible tablets, rapimelts, pFastus tablets, quick dissolving tablet.

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

- FDTs should have an *in vitro* disintegration time of approximately 30sec or less.
- Generally, the FDT 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 FDT for both patients and regulators.
- The guidance serves to define the upper limits of the FDT 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 FDT.

Need To Develop Fdt

The need for one of the non-invasive delivery system i.e., Fastly 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

Fastly 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 Fast 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 Fast 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.

Mechanism Of Action

The FDT is placed upon patient's tongue or any Fastmucosal 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 Fastmucosal absorption.

Advantages Of Fdts: Advantages of FDTs include:

- Ease of administration to geriatric, paediatric, mentally disabled, and bed-ridden patients, who have difficulty in swallowing the tablet.

- The FDTs 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 Fast, 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 Fast cavity.
- Good Fast 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 FDTs 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 Fast.[3]

Limitations To Fastdispersible Tablets

- Drugs with relatively larger doses are difficult to formulate into FDTs 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 FDTS**.**

Desired Characteristics And Challenges To Develop Fast Dispersible Tablets.

Rapid Disintegration: Rapid disintegration is a desired characteristic of FDT where it rapidly disintegrates in Fast in matter of seconds. Selection of super disintegrants which tends the drug to release fast is a challenging part of formulation scientist.

Palatability: As most of the drugs are bitter in taste or tasteless, effective taste masking technology should be adopted to develop Fastdispersible tablet as they disintegrate or dissolve in patient's Fast cavity. Hence taste masking of Fastdispersible tablets becomes challenging as well as a desired characteristic for better Fast feel and patient's compliance.

Mechanical Strength: The Fastdispersible tablet should be formulated in such a way that it disintegrates rapidly in fraction of seconds in Fast cavity which is a desired characteristic for patients who have swallowing problem and should hold the mechanical integrity of tablet to avoid friability and special packing which is challenging to formulators.

Hygroscopicity: Several Fastly disintegrating dosage forms are hygroscopic and cannot maintain physical integrity under normal conditions of temperature and humidity. Hence, the formulators should develop a system to maintain low sensitivity to environment conditions which is a challenging as well as desired character to attain.

Amount Of Drug: The amount of drug incorporated as an Fastdispersible tablet should give sufficient response as well as it must be lower than 400mg for insoluble drugs and less than 60 mg for soluble drugs.

Size Of The Tablet: The degree of ease when taking a tablet depends on its size. The size of the tablet should be such that it should be easy to swallow and to handle and for good packing.

MATERIALS

Haloperidol-Procured From Mylan Laboratories Ltd., New Delhi. Provided by SURA LABS, Dilsukhnagar, Hyderabad, Sodium croscarmellose-Merck Specialities Pvt Ltd, Mumbai, India, Crospovidone-Merck Specialities Pvt Ltd, Mumbai, India, Sodium starch glycolate-Merck Specialities Pvt Ltd, Mumbai, India, Aspartame-Merck Specialities Pvt Ltd, Mumbai, India, Mg stearate-Merck Specialities Pvt Ltd, Mumbai, India, Aerosil-Merck Specialities Pvt Ltd, Mumbai, India, Talc-Merck Specialities Pvt Ltd, Mumbai, India, Mannitol-Merck Specialities Pvt Ltd, Mumbai, India

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 Haloperidol

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 λmax was found to be 245 nm. Hence all further investigations were carried out at the same wavelength.

b) Construction of standard graph

100 mg of Haloperidol 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 0.2 ml, 0.4ml, 0.6ml, 0.8ml and 1.0ml, 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 2,4,6,8 and 10µg/ml respectively. The absorbance of each concentration was measured at respective (λmax) i.e,245nm.

Formulation development

- Drug and different concentrations of super disintegrants (Sodium croscarmellose, Crospovidone, 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 (Aerosil) 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 1: Formulation table showing various compositions

Ingredients	H1	H2	H3	H4	H5	H6	H7	H8	H9
Haloperidol	5	5	5	5	5	5	5	5	5
Sodium croscarmellose	5	10	15	-	-	-	-	-	-
Crospovidone	-	-	-	5	10	15	-	-	-
Sodium starch glycolate	-	-	-	-	-	-	5	10	15
Aspartame	5	5	5	5	5	5	5	5	5
Mg stearate	5	5	5	5	5	5	5	5	5
Aerosil	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Mannitol	74	69	64	74	69	64	74	69	64
Total Weight	100	100	100	100	100	100	100	100	100

The tablets were prepared by using tablet Direct compression machine. The hardness of the tablet was maintained as 2.45 to 2.63 kg/cm^2

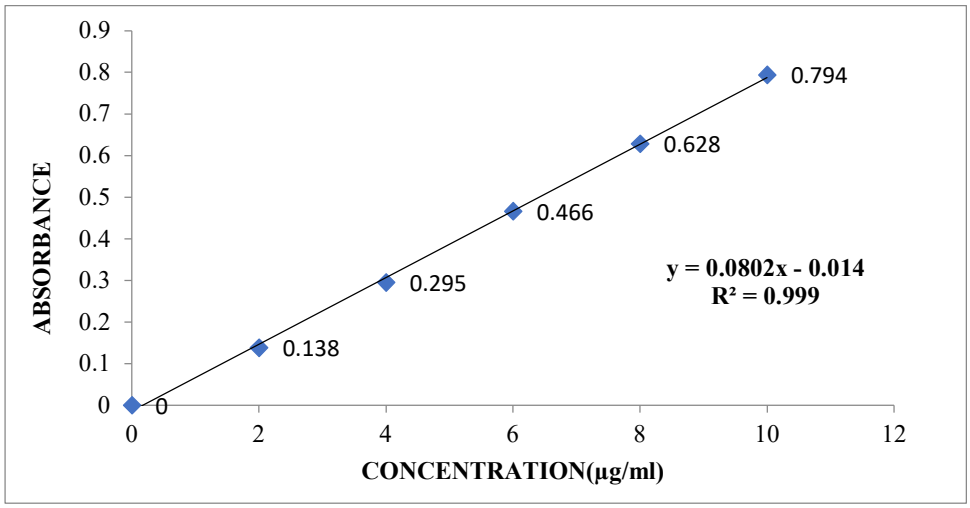
RESULTS AND DISCUSSION

Preparation Of Calibration Curve Of Haloperidol

The Regression Coefficient was found to be 0.999 which indicates a linearity with an equation of y = 0.0802x - 0.014. Hence beer - Lambert's law was obeyed.

Table 2: Calibration curve data of Haloperidol in ph 6.8 phosphate buffer

Concentration (µg/mL)	Absorbance
0	0
2	0.138
4	0.295
6	0.466
8	0.628
10	0.794



Evaluation of pre - compression parameters of powder blend

Table 3: 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
H1	27.52	0.52	0.65	18	1.21
H2	28.87	0.51	0.62	17	1.21
H3	30.02	0.53	0.63	15	1.20
H4	30.01	0.53	0.64	17	1.20
H5	28.43	0.50	0.63	20	1.26
H6	28.26	0.55	0.65	15	1.14
H7	28.85	0.51	0.62	17	1.21
H8	30.14	0.52	0.63	17	1.21
H9	28.04	0.54	0.65	16	1.20

- 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 (0.50 - 0.55**)** and tapped density was in range of (0.62 **-** 0.65.
- The carr's index and hausner's ratio was calculated from tapped density and bulk density.

Evaluations of post compression parameters of maprotiline FDTS

Table 4: Evaluation of post compression parameters of Haloperidol Fast dissolving tablets

Formulation codes	Average Weight (mg)	Hardness (kg/cm^2)	Friability (%loss)	Thickness (mm)	Drug content (%)	*In vitro* Disintegration Time (min)
H1	99.41	2.57	0.26	1.88	98.12	6.18
H2	98.39	2.62	0.35	1.75	99.28	7.21
H3	99.56	2.53	0.29	1.53	97.84	8.34
H4	97.47	2.48	0.34	1.68	100.62	7.35
H5	96.38	2.51	0.24	1.51	101.31	6.89
H6	100.12	2.45	0.21	1.62	100.08	5.22
H7	101.22	2.63	0.33	1.55	98.22	7.12
H8	98.08	2.58	0.39	1.83	98.47	8.36
H9	99.23	2.55	0.25	1.77	99.35	7.22

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 FDT formulations were evaluated for their hardness, using monsanto hardness tester and the results are shown above. The average hardness for all the formulations was found to be between (2.45 to 2.63) Kg/cm^2 which was found to be acceptable. Friability was determined to evaluate the ability of the tablets to withstand the abrasion during packing, handling and transporting. All the FDT 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 **0.21 to 0.39**, which was found to be within the limit. Addition of Aerosil resulted in appreciable decrease in friability.

Drug content

All the 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 the formulations were found to be in the range of **(97.84 to 101.31).** 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 FDT formulations comply with the standards given in IP.

***In vitro* disintegration time**

In vitro disintegration studies showed from 5.22 to 8.36 Minutes. The H6 Formulation showed Very Less *In vitro* Disintegration Time i.e., 5.22 Minutes.

***In vitro* drug release studies of haloperidol**

Table 5: Dissolution data of Haloperidol

TIME (minutes)	H1	H2	H3	H4	H5	H6	H7	H8	H9
0	0	0	0	0	0	0	0	0	0
5	35.6	46.51	55.67	52.69	45.34	54.42	52.26	55.38	54.18
10	49.36	62.45	65.44	65.12	60.49	66.87	65.86	63.99	69.85
15	68.32	77.86	76.56	79.16	78.15	74.43	74.97	79.12	80.49
20	74.58	85.2	83.69	86.45	85.25	86.86	82.67	89.2	90.23
30	85.36	93.64	94.61	96.27	97.2	99.25	89.49	91.52	95.79

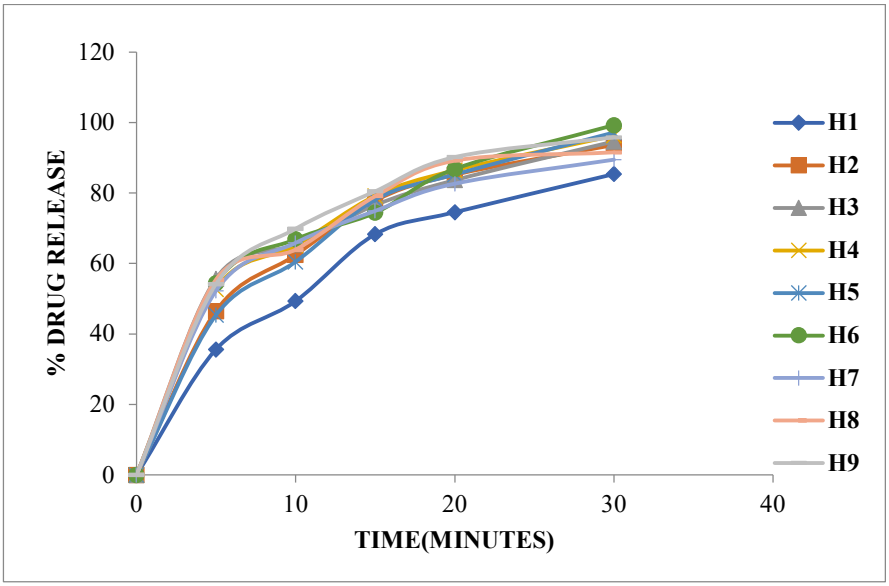


Fig 1: Dissolution profile of all formulations H1- H9

Formulations prepared with Sodium croscarmellose showed maximum drug release i.e., 94.61% (H3Formulation) at 30 min in 15 mg of blend. Formulations prepared with Crospovidone showed maximum drug release i.e., 99.25% (H6 Formulation) at 30 min in 15 mg of blend. Formulations prepared with Sodium starch glycolate showed maximum drug release i.e., 95.79% (H9 Formulation) at 30 min in 15 mg of blend. Among all formulations H6 formulation considered as optimised formulation which showed maximum drug release at 30 min. i.e. 99.25%. Crospovidone were showed good release when compared to Sodium croscarmellose, Sodium starch glycolate. finally concluded that H6 formulation (Contains Crospovidone) was optimised better formulation.

FTIR results

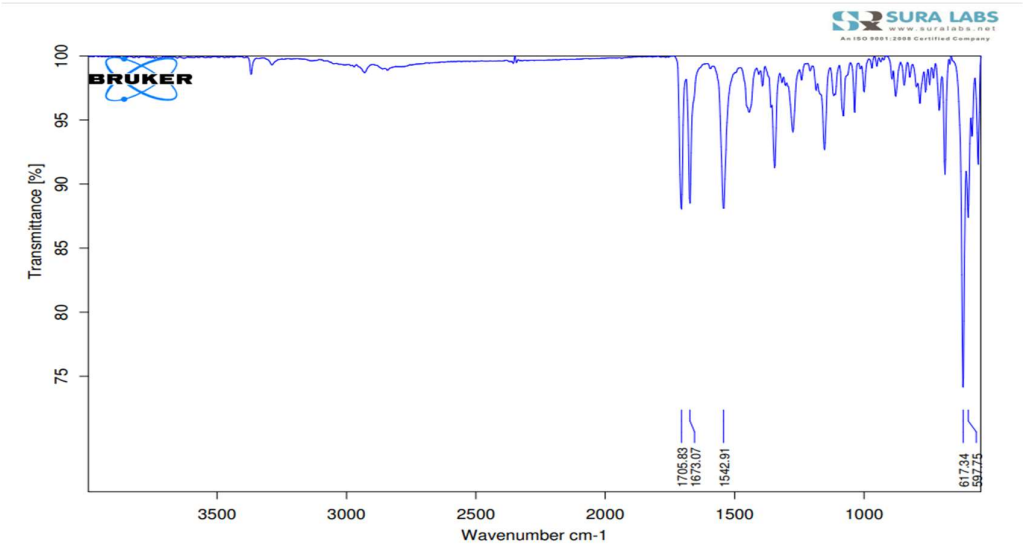


Fig 2: FTIR of Haloperidol Pure drug

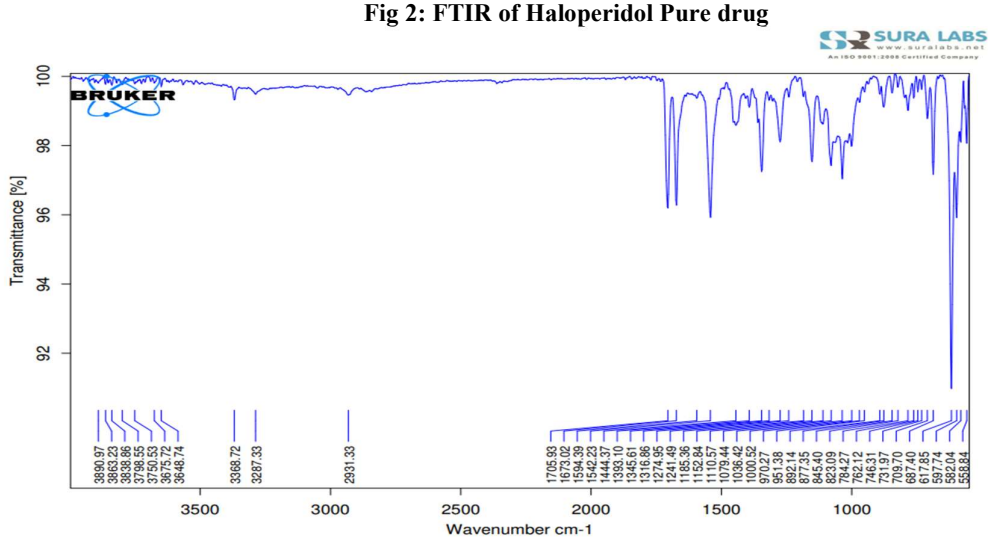


Fig 3: FTIR of Haloperidol optimized Formulation

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

CONCLUSION

In the present work Fast Dissolving tablets of Haloperidol were prepared by direct compression methods using super disintegrates such as Sodium croscarmellose, Crospovidone and Sodium starch glycolate. All the

tablets of Haloperidol were subjected to tests for weight variation, hardness, friability, in vitro dissolution, drug content uniformity.

Based on the above studies the following conclusion can be drawn: Tablets prepared by direct compression methods were found to be good and free from chipping and capping. The hardness of the prepared tablets was found to be in range of 2.45 to 2.63 kg/cm^2 , The friability values of the prepared tablets were found to be less than 1%. The FT-IR studies indicated that the drug and excipients was no interaction between them. Based on the In vitro dissolution studies H6 showed 99.25% for 30mints. The drug content of tablets was uniform across all batches ranging from 97.84 to 101.31%.

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