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ORIGINAL ARTICLE

Formulation and Evaluation of Orodispersible Tablet of Warfarin by Direct Compression Technique

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ABSTRACT
The demand for development of oral dispersible tablets (ODTs) has enormously increased as it has significant impact on the patient compliance. The aim of this investigation was to prepare orodispersible tablets of Warfarin using various concentrations of superdisintegrants agents like Polyplasdon XL, Crospovidone CL, Prosolv ODT by direct compression method. Four Tablets formulations having superdisintegrants at different concentration levels were prepared. These tablets were evaluated for weight variation, friability, hardness, drug content, and in vitro disintegration time. In vitro release studies that almost 100% of drug was release from all the formulations were within 15 minutes. Formulation F2 showed faster drug release 103.9±0.2 within 15 minutes in comparison to other formulation so it is selected as optimized batch. It was concluded that Orodispersible Tablets of Warfarin can be prepared successfully by direct compression methods as it satisfies all the criteria as mouth dissolving tablet and would be alternative to the currently available conventional tablets.
Keywords: *Warfarin,Direct Compression, Orodispersible tablets, Crospovidone, Disintegration time.*

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INTRODUCTION

The demand for development of oral dispersible tablets (ODTs) has enormously increased as it has significant impact on the patient compliance [1]. Oral dispersible tablets offer an advantage for populations who have difficulty in swallowing [2]. 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 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 [3-5]. ODTs with good taste and flavor increase the acceptability of bitter drugs by various groups of population

United States Food and drug administration defined fast disintegrating tablet as "a solid dosage form containing medicinal substance or active ingredient which disintegrate fast usually within a few seconds when placed upon the tongue [6-9]." FDTs differ from traditional tablets as they are designed to be dissolved on the tongue rather than swallowed whole. Orodispersible Tablets are also known as mouth disintegrating tablets, melt-in mouth tablets, Orodispersible tablets, porous tablets, quick dissolving tablets, fast dissolving tablets[10-12].

MATERIAL AND METHODS

Warfarin was obtained as a gift sample Maxheal Pharmaceuticals, MIDC, Nashik Polyplasdon XL, Crospovidone CL, Prosolv ODT, Avicel PH 102, PVP K30, Avicel PH 102, Orange ,Mannitol, Aspartame ,Mg. stearate, Colloidal Silicon Dioxide. From Research Lab Fine Chem. Ltd. Mumbai.

METHODS: [13-15].

Preformulation Study

Identification of Drug

Identification of drug was carried out by melting point determination, Infrared spectroscopy, differential scanning calorimetry (DSC) and UV spectroscopy.

A) Melting point method

Melting point method is important for confirmation of drug. In this method temperature was noted at which point sample start to melt. For this drug whose analysis is to be carried out was filled into capillary tube and tied in such a way it remains dipped in liquid paraffin bath and melting range was noted.

B) UV Spectrophotometer

10 mg of API was dissolved in 100 ml of the pH 5.8 phosphate buffer to obtain the working standard of 100 µg/ml. Aliquots of 0.1 ml to 0.6 ml from the stock solution representing 1 to 6 µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with pH 5.8 phosphate buffer. The Absorbance's of the above solutions were taken at λmax 243 nm against the blank solution prepared in the same manner without adding the drug. Hence when the UV spectrum of drug solution in pH 5.8 phosphate buffer was scanned at 400 nm to 200 nm, maximum absorbance was observed at 243 nm.

C) Infrared Spectroscopy

IR spectrum of drug was measured in the solid state as potassium bromide dispersion. FTIR spectra of a drug were obtained using a FTIR spectrometer (8400S, Shimadzu, Japan). The sample was previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:100 (sample: KBr) ratio, respectively. The pellets were prepared by compressing the powders, under force of 12 tones for 5 min in a hydraulic pressed and IR was taken.

D) DSC

Melting point of drug was determined using DSC. Thermograms for a drug was obtained using DSC (Metller Dsc 1 Star System,Zurich, Switzerland).

E) Solubility study

Solubility is a useful parameter mainly for poorly soluble drugs. Bioavailability problems are often present, when the solubility of a drug is less than 10 mg/ml over the pH range 1-8. Drug solubility was determined by preparing saturated drug solutions in various buffer medium, maintained at 37°C ± 0.5°C in a water bath and continually shaken the sample on to mechanical shaker up to 24 h. Withdrawn samples were filtered through a whatmann filter paper, and assayed by UV spectrophotometer at 243 nm.

F) Drug -Excipients Interaction Study

Drug-excipients interaction study was carried out by using Fourier Transform Infrared spectroscopy (FTIR) and differential scanning Calorimetry (DSC).

a) Fourier Transform Infrared (FTIR) Spectroscopy

Infrared spectroscopy was used to predict possible drug – excipients interaction. IR spectrum of drug was measured in the solid state as potassium bromide dispersion. For that drug, polymers and physical mixture were filled in prewashed and dried ampoules and sealed with aluminum paper. The sealed ampoules were kept at 37 ± 0.5 °C for 28 days in stability chamber. After one month stability period ampoules were taken from the stability cabinet and test samples were subjected to FTIR by preparing transparent pellets with potassium bromide (KBr) in ratio of 1:100 test sample to KBr.

b) Differential scanning calorimetry (DSC)

Drug, polymers and physical mixtures were filled in the prewashed and dried ampoules followed by sealing. The sealed ampoules were kept at 37 ± 0.5°C for 28 days in stability chamber. At the end of 28 days, ampoules were removed from stability chamber and proceed for interaction study. Drug-polymer and other excipients interaction study was carried out by using DSC. In this, study thermograms of pure drug, physical mixture of core pellets, were taken. Heating was done at a scan rate of 10°C/min.

G) Determination of Calibration curve of API in pH 5.8 buffer

10 mg of API was dissolved in 100 ml of the pH 5.8 phosphate buffer to obtain the working standard of 100 µg/ml. Aliquots of 0.1 ml to 0.6 ml from the stock solution representing 1 to 6 µg/ml of drug were transferred to 10 ml volumetric flask and the volume was adjusted to 10 ml with pH 5.8 phosphate buffer. The absorbance's of the above solutions were taken at λmax 243 nm against the blank solution prepared in the same manner without adding the drug. A graph of absorbance Vs concentration was plotted and was found to be linear over a range of 1 to 6 µg/ml indicating its compliance with Beer's lambart law.

FORMULATION OF ORO DISPERSIBLE TABLETS

Weighted and sifted the dry complex by #30 sieves. Warfarin, Diluents (Mannitol, Avicel PH 102) and superdisintegrant (Crospovidone CL, Polyplasdone XL) passed through #40 sieve and Colloidal Silicon Dioxide, Sweetner, Flavors, Lubricant was passed through #60 sieve. Then Mixed all the ingredient in poly begs for 5 min &Lubricated blend were compressed into tablets using 12mm FFBE (Flat Face Bevel Edge) punch set using a eight station tablet press. Compression was carried out using "B" tooling punches sets [16-18].

Table 1: Composition of Oral Orodispersible Tablets of Warfarin

Sr. No.	Ingredients (mg)	F1 (mg/tab)	F2 (mg/tab)	F3 (mg/tab)	F4 (mg/tab)
1.	Warfarin	250	250	250	250
2.	Prosolv ODT	227.5	127.5	-	-
3.	Avicel PH 102	-	100	100	100
4.	PVP K30	-	-	25	25
5.	Crospovidon CL	-	-	25	-
6.	Polyplasdon XL	-	-	-	25
7.	Mannitol	-	-	55	55
8.	Colloidal Silicon Dioxide	-	-	5	5
9.	Aspartame	10	10	25	25
10.	Orange	10	10	10	10
11.	Magnesium Stearate	2.5	2.5	5	5
	Net Total	500.00	500.00	500.00	500.00

***All the quantities mentioned above in mg**

Evaluation of prepared Tablets: [19-20].

Prepared Orodispersible tablets were evaluated for the following parameters.

Physical appearance

The general appearance and elegance of tablet was identified visually, which include tablet size, shape, color, presence or absence of an odor, taste, surface texture and sticking of tablet etc.

Content Uniformity

For this at least 20 tablets were randomly selected. 20 tablets were crushed into fine powder and assayed individually; the content uniformity of drug should be within 90% to 110% of the labeled claim

Hardness

Tablets require certain amount of strength or hardness, to withstand mechanical shocks of handling in manufacture, packaging, and shipping. The most widely used apparatus to measure tablet hardness (crushing strength) is the Schleuniger hardness tester.

Method: Ten tablets were randomly selected and hardness was measured in Schleuniger hardness tester. The average of 3 readings was taken as hardness of the tablet.

Thickness

Ten Tablets were selected randomly from individual formulations and thickness was measured by using vernier caliper scale, which permits accurate measurement. The average of 3 readings was taken as thickness of the tablet.

Friability

Friability is related to the ability of tablet to withstand both shocks and abrasion without crumbling during manufacturing, packing, transportation and consumer handling. Friability can be evaluated by means of friability test apparatus (The Roche friabilator). Compressed tablets that loose less than 0.5% to 1.0% in weight are generally considered as acceptable.

Method: Ten tablets were randomly select and weighed (initial wt.) and then transfer into Rocha friabilator. It was subjected to 100 revolutions in 4 minutes. The tablets were dedusted and reweighed (final wt). These two weights (i.e. initial and final) were applied to calculate the friability of tablet.

$$\% \text{ Friability} = \frac{\text{(Initial Weight – final weight)}}{\text{(Initial weight)}} \times 100$$

Weight variation

Twenty tablets were taken randomly, weigh individually and average weight was determined. The individual tablet weight was compared with average tablet weight.

Disintegration test

In vitro disintegration time was measured using USP disintegration test apparatus. For DT test randomly six tablets were selected from each batch and test was performed in 900 ml distilled water at 37 ± 0.5 °C temperature and at the rate of 30 ± 2 cycles/min.

Dissolution study

Medium: pH 5.8 phosphate buffer (see Buffer Solutions in the section 900 mL.USP II apparatus at 50 rpm.

Time: 30 minutes.

Procedure - One tablet was placed in each dissolution vessel and the paddle rotation speed was set at 50rpm. 10ml of the sample was withdrawn at the intervals of 0, 5, 10, 15, 30 min and the same volume of the fresh medium was replaced every time. The samples were analyzed for drug content at a wavelength

of 243 nm using double beam UV-Visible spectrophotometer. The content of the drug was calculated using the equation generated from the standard curve. The percentage cumulative drug released was calculated.

RESULT AND DISCUSSION

Preformulation study

Identification of Drug

Confirmation or identification of drug test was carried out by UV, IR , DSC and melting point method.

UV Spectroscopy

Drug solution was scanned at 200-400 nm, maxima was observed at 243 nm as shown in Figure 1. This was confirmed with reported UV spectrum of the reference.

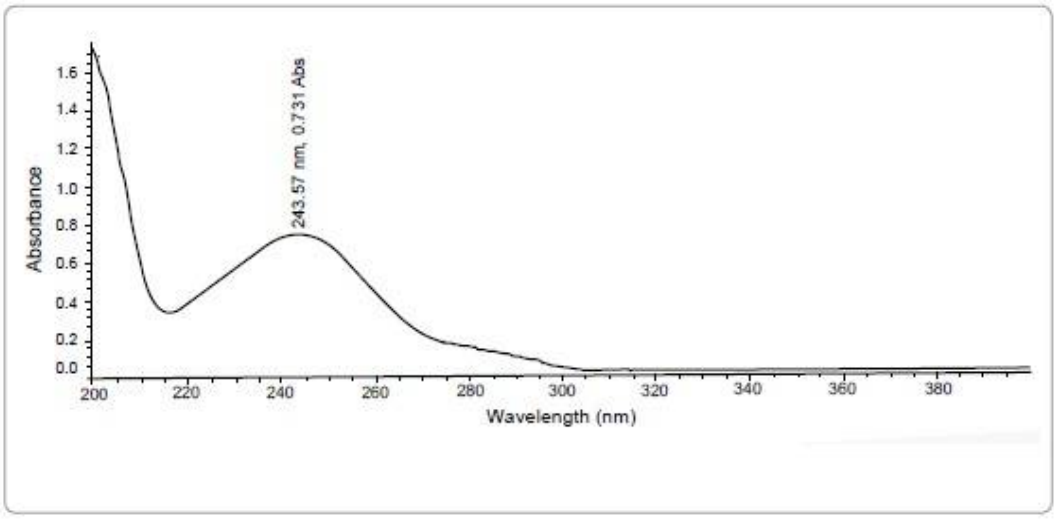

Fig 1: UV Spectrum of Warfarin

IR Spectroscopy

An infrared (IR) spectrum of API was taken by using the KBr disk method (1 mg sample in 100 mg KBr). The scanning range was 450 to 4000 cm $^{-1}$ and the resolution was obtained 1 cm $^{-1}$.

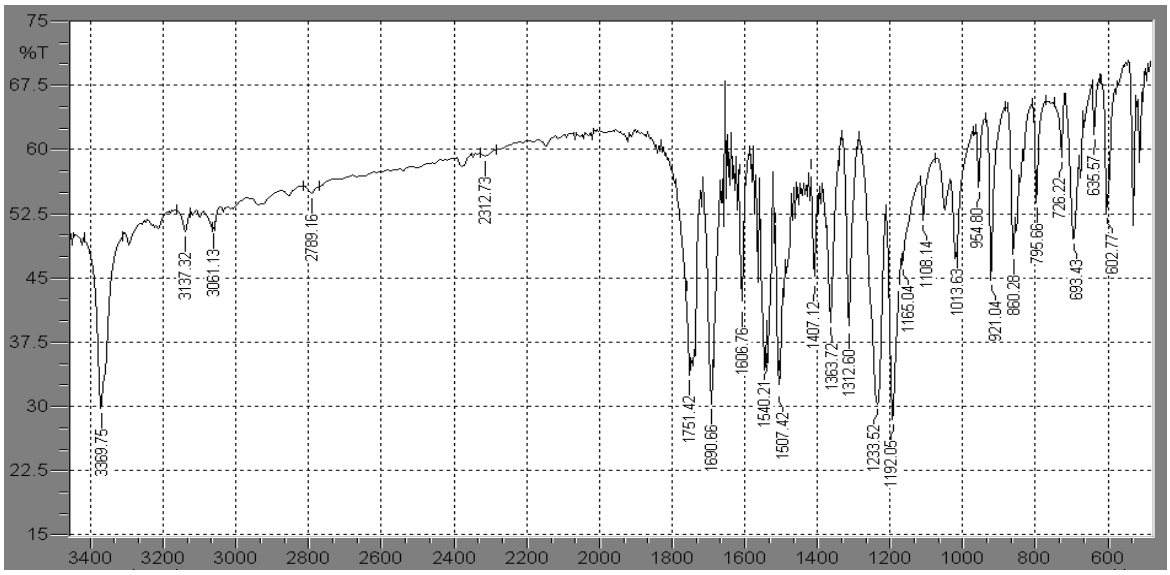

Fig 2: IR Spectra of API (Warfarin)

Differential Scanning Calorimetry

API was confirmed by DSC by keeping the heating rate of 1ºC/min.The thermogram of API exhibited sharp endothermic peak with onset temp 165.65 ºC and peak temp 169.62ºC as shown in fig 3 which was reported in literature.

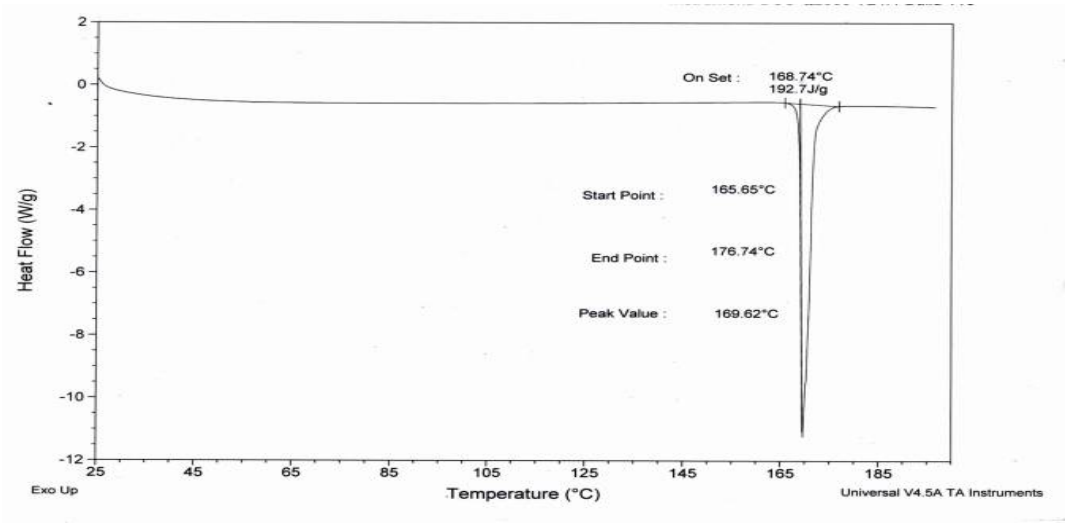

Fig 3: DSC Curve of API

Melting Point Determination

Melting point of drug was measured; and found to be in the range of 151-160^{o}C. It was confirmed with the reported melting point of reference.

Drug- Excipient Interaction study

IR

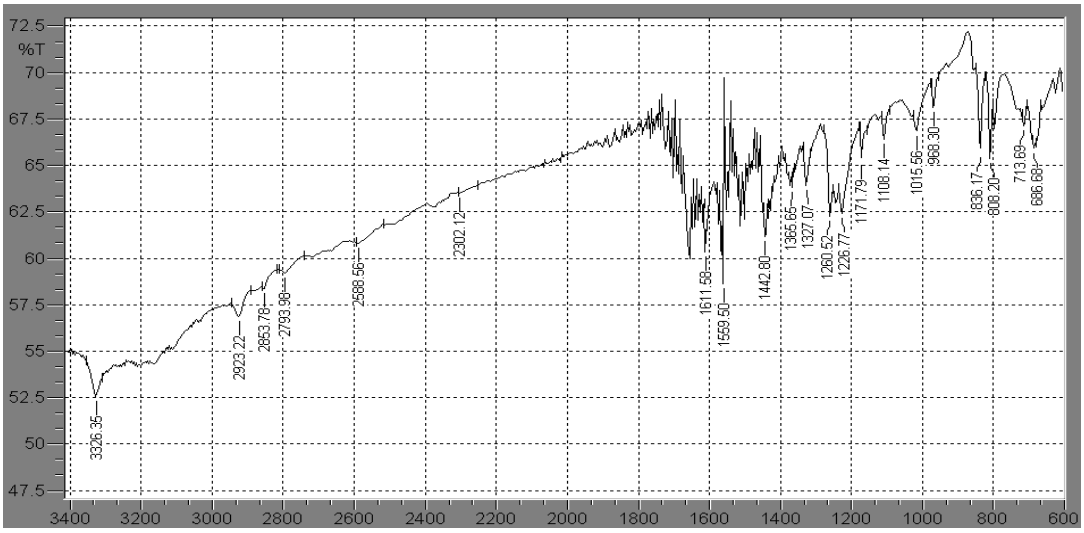

Fig 4: IR spectra of API (Warfarin) + Excipient physical mixture

An IR spectrum of API was already shown in fig:2 and an IR spectra of drug- excipient physical mixture were reported in fig. 4. The FT-IR studies were conducted to ensure interactions among the Warfarin and excipients used in the formulation. The same peaks were also observed in the formulation indicating the stable nature of the drug. All the physical mixtures of Warfarin and individual excipients show insignificant changes in actual peaks. Warfarin showed prominent peaks at 795.66, 921.04, 1233.52, 1507.42, and 1690.66 due to the presence of C-Cl alkyl halides, O-H carboxylic acid, C-N aliphatic amines, N-O nitro group and C=O stretch Ester. The same peaks with little difference were observed in the formulation indicating the stable nature of the drug. No change in the peak of drug indicates that there was no drug-excipient interaction between Warfarin and excipients which were used in formulation of orally disintegrating tablet (ODT).

Differential scanning calorimetry (DSC)

Diffractogram of drug was already shown in fig: 3 and diffractogram of drug- excipient were reported in fig. 5.

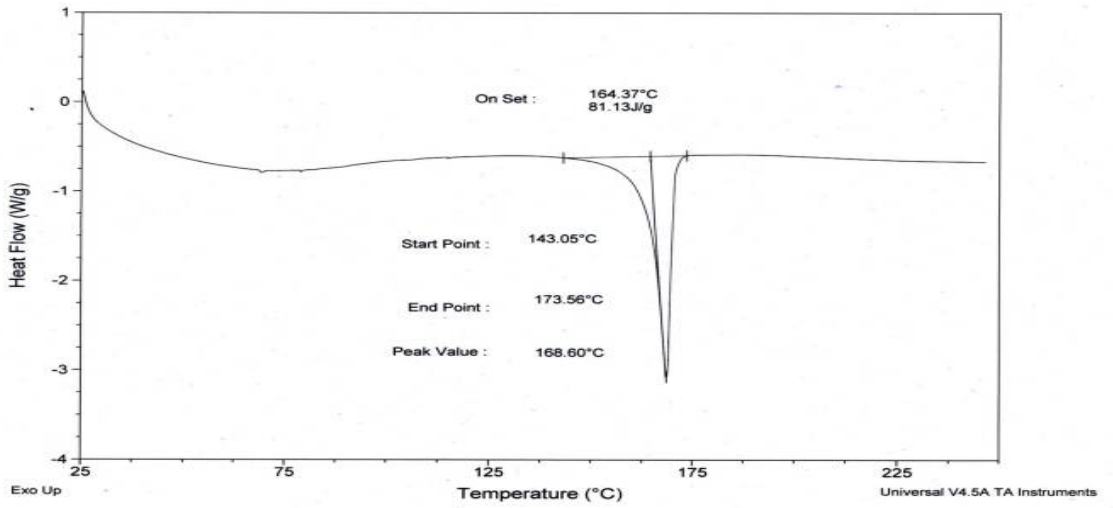

Fig 5: DSC of API + Excipient physical mixture

Analysis of Drug

Solubility of Drug

The solubility of Drug in different media is reported in Table no. 11 from the result obtained we conclude that the solubility of drug is depicted in table.

Table 2: Results of solubility study

Sr. No.	Dissolution media 37°C	Solubility(mg/ml)
1.	Purified Water	12.0
2.	0.1N Hydrochloric Acid	14.5
3.	Acetate Buffer pH 4.5	13.6
4.	Phosphate Buffer pH 5.8	14.1

Calibration curve of API in pH 5.8 buffer

Table 3: Calibration curve API in 5.8 pH buffer

Sr. No.	Concentration (µg/ml)	Absorbance
1	0	0.0
2	2	0.212
3	4	0.476
4	6	0.689
5	8	0.927

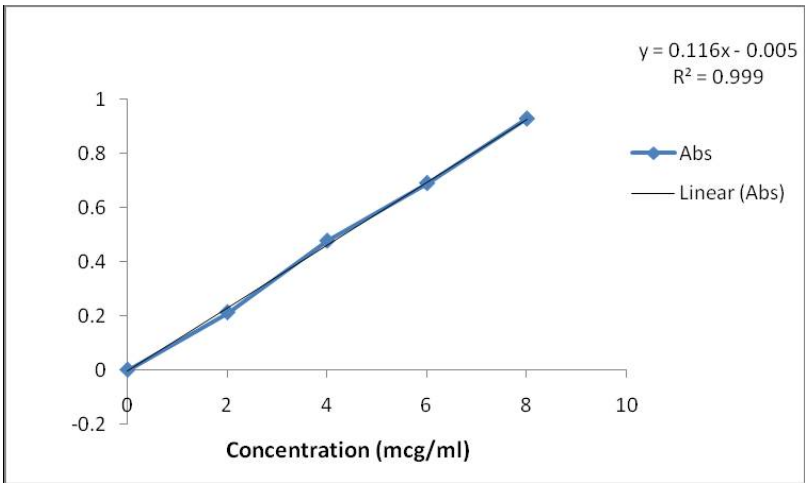

Fig 6: Calibration curve of API in PH 5.8 buffer

EVALUATION OF ORODISPERSIBLE TABLETS.

Table 4: Physical Parameter of batch F1 to F4

Batch	Weight variation(mg)	Hardness (kp)	Disintegrating time (sec)	Friability (%)
F1	499	2.0-3.0	22	0.49
F2	503	2.0-3.0	13	0.36
F3	500	2.5-3.5	21	0.19
F4	497	2.5-3.5	15	0.16

Physical appearance

The general appearance and elegance of tablet was identified visually ,prepared tablets have absence of an odor, , smooth surface texture and no sticking seen in tablet etc.

Weight variation

The weight of all the tablets was found within the range of 500 ± 3 mg. Hence, the weight of all formulations was found within the limit

Hardness,

Hardness of the formulations F1-F4 was observed within the range of 2.0-3.0 to 2.5-3.5kg/cm2 as shown in Table 4.

Thickness

The thickness of all the tablets was found within the range 5.88±0.2 to 5.46±0.5mm.

Friability

The percent friability of all the prepared formulae was <1%. The previous results indicated that all formulations complied with the pharmacopeias limits for these tests.

Drug content: The drug content was found to be uniform for all the prepared formulations and was found to be within the range of 97.34 to 99.90%.

Disintegration test: From the in vitro disintegration test, (F2) has lower disintegration time (11seconds).

***In vitro* Dissolution test:** Based on the dissolution data of all the prepared ODTs, the F2 batch shows 103.9±0.2% drug release in 15minutes. So F2 is selected as optimized batch.

***In vitro* dissolution study:**

Table 5: Dissolution study of Batch F1 to F4

Time (Mints)	F1	F2	F3	F4
0	0.00	0.00	0.00	0.00
5	85.8±0.8	89.9±0.3	90.7±0.4	85.9±0.5
10	96.9±0.9	99.8±0.4	98.9±0.9	96.5±0.4
15	101.2±0.5	103.9±0.2	100.2±0.8	100.7±0.7
20	102.8±0.4	104.6±0.8	102.9±0.6	102.1±0.6
30	102.9±0.6	104.9±0.2	105.7±0.7	108.8±0.2

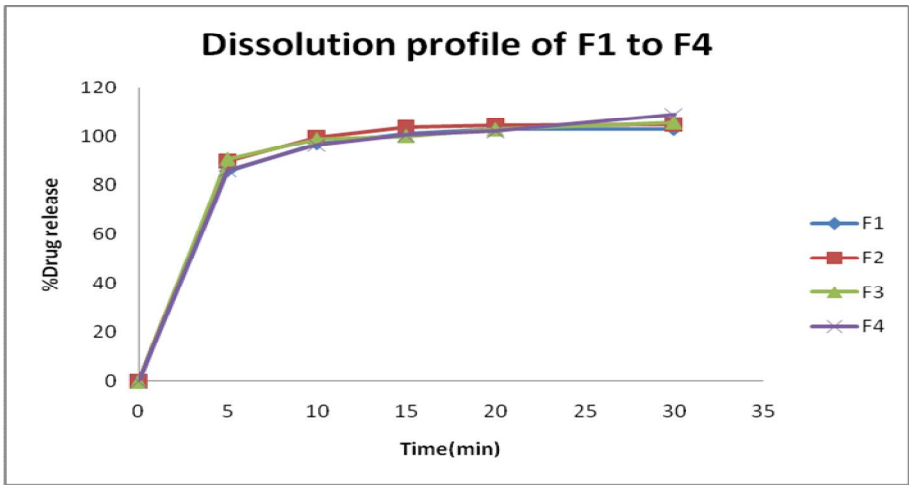

Fig 7: Dissolution profile of batch F1 to F4

CONCLUSION

The Orodispersible Tablets of Warfarin were prepared by direct compression method using using various concentrations of Super disintegrant agents like Polyplasdon XL, Crospovidone CL, Prosolv ODT.The FTIR ,DSC analysis revealed that the Super disintegrant used were compatible with Warfarin. In vitro release studies that almost 100% of drug was release from all the formulation were within 15 minutes. Formulation F2 showed faster drug release 103.9±0.2 within 15 minutes in comparison to other formulation so it is selected as optimized batch. It was concluded that Orodispersible Tablets of Warfarin can be prepared successfully by direct compression methods as it satisfies all the criteria as mouth dissolving tablet and would be alternative to the currently available conventional tablets.

DECLARATION OF COMPETING INTERESTS

The authors have declared that no competing interest exists".

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