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Development of Fast Dissolving Tablets Containing Fexofenadine Hydrochloride Prepared by Lyophilization Technique

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Abstract: Objectives: To improve the aqueous solubility and dissolution of fexofenadine HCl, an attempt was made to prepare its fast dissolving tablets by lyophilization technique. Methods: For the preparation of lyophilized tablets (F1-F32), the drug was dispersed in a hydrated solution of water-soluble polymers (gelatin/maltodextrin/acacia) containing glycine and mannitol. The blend was pelted down into the patches of a blister pack, frozen down and then lyophilized. Different characterization parameters viz. differential scanning calorimetry, hardness, weight variation, X-ray diffraction (XRD), scanning electron microscopy (SEM), mercury porosimetry, solubility, wetting time and water absorption ratio, lyophilization tablet index, drug content, *in vitro* dissolution and stability were evaluated. Key findings: Tablets (F32) containing acacia were found to have fast disintegration and relatively higher mechanical strength with improved drug solubility. X-ray diffractogram and scanning electron micrograph indicated decrease in crystallinity of drug and a good porous structure property for prepared tablet, respectively. Dissolution study showed complete drug released within 5 min. Moreover, tablets (F32) were found to be stable for one month at 25 ± 2 °C/60 ± 5% relative humidity.

Key words: Lyophilization, fexofenadine HCl, SEM, XRD, lyophilized tablet index (LTI), mercury porosimetry, wetting time.

1. Introduction

Tablet is considered to be the most extensively used unit dosage form for oral administration due to ease of its self-administration, compactness, and simplicity in manufacturing. But, geriatric and paediatric patients as well as patients with swallowing problem might possess poor patient compliance with such administration. To tackle this problem, researchers have tried unconventional formulations such as “melt in mouth” or “mouth dissolve (MD)” tablets or “fast dissolving tablets (FDTs)”. According to European pharmacopoeia, FDTs are those formulations, when administered orally, dispersed on the tongue within 3 min [1-6]. Such FDTs disperse and dissolve briskly in saliva within a few seconds to minutes even if there is no water available. They are also found useful to the bedridden patients and to active working patients who are devoid ready access to water due to their busy schedule or travelling [7].

Lyophilization, tablet moulding, direct compression method, spray drying, and sublimation technology are majorly used technologies to prepare FDTs. Amongst these, lyophilization or freeze-drying process has got some added advantages like suitability for heat-sensitive products, enhanced product stability, ease of reconstitution and great mouthfeel due to fast melting effect [8-14]. These tablets are prepared by sublimation of water contained in it post freezing, making them highly porous and amorphous. Such tablets spontaneously dissolved in the saliva within seconds can lead to the fast absorption and quick inception of action [15].

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BCS class II drugs are suffering from a major problem of poor aqueous solubility, which affects their absorption process and ultimately leads to poor bioavailability. Thus, they usually require high doses to reach therapeutic plasma concentrations post oral administration considering their extensive first-pass metabolism. Augmentation in the magnitude and rate of dissolution is worth for such compounds. To nullify such problems associated with poorly water-soluble drugs like flutamide, ibuprofen, ketoprofen, olanzapine, fexofenadine HCl (FXD), etc., the utilization of lyophilization technique has added advantages as well [16].

Fexofenadine HCl, a BCS class II drug, indicated for the symptomatic relief of seasonal allergic rhinitis and for the treatment of elementary skin manifestations of chronic idiopathic urticaria. These conditions are commonly found in pediatric patients, where palatability is of main concern. FXD has been shown to have potent antiallergic or antihistaminic activities similar to levocetirizine and desloratadine with an advantage that it does not cross the blood-brain barrier to any appreciable degree. Thus, it has better safety as compared to levocetirizine and desloratadine [17-22]. However, a major limitation of FXD is its water solubility which may result in poor dissolution and low bioavailability [23-24]. In the light of above facts, in the present investigation, lyophilization technique was employed to prepare FDTs of FXD to achieve better patient compliance, enhanced bioavailability, instant onset of action, reduced first-pass metabolism, convenience in administration and good mouthfeel [25].

2. Materials and Methods

2.1 Materials

FXD was obtained as a gratis sample from Aventis Pharma Ltd., Ankleshwar. Gelatin was purchased from Krishna-Chemical Industry, Vadodara and remaining all ingredients were purchased from Chem Dyes Corporation, Vadodara.

2.2 Methods

2.2.1 Identification of Drug

Melting Point Determination. Melting point of drug was determined by Thiele's tube method. A capillary was taken and one of its ends was sealed by burning over flame. Drug crystals were filled into it about 2-3 mm height with a sealed end. It was then tied to a thermometer so that the drug crystals would be next to a thermometer bulb. The thermometer along with a capillary tube was placed in the Thiele's tube filled with liquid paraffin. Over a small flame, this assembly was heated and observed for melting of crystals. Average of the temperatures at which the crystals first begun to melt and at the last portion finished melting was noted down known as the melting point.

Fourier Transformation Infrared (FTIR) Spectra. FTIR spectra of the drug were obtained by scanning prepared disc with KBr in the range from 4,000-400 cm^{-1} using FTIR spectrophotometer (Perkin Elmer, Spectrum GX FTIR).

2.2.2 The Drug-Excipients Compatibility Studies

Differential scanning calorimetry (DSC) study was used to evaluate drug-excipient interaction. Weighed sample (5-8 mg) of FXD and physical mixture of FXD and additives (1:1) were subjected to DSC-60 instrument (Perkin Elmer Pyrisl) to get DSC thermogram.

2.2.3 Preparation of FDTs

Matrix-forming polymer (gelatin/maltodextrin/acacia) was dissolved in distilled water by stirring on mechanical stirrer to get a clear solution (% *w*/*v*). Glycine (30% *w*/*w* of total solid content) and mannitol (1% *w*/*w* of total solid content) were added to the above solution with continuous stirring so that they make a clear solution. To this mixture, an accurately weighed FXD was added to achieve 60 mg per mL drug concentration. One mL of this solution was poured into each patch of the tablet blister pack to get 60 mg of drug in each pocket (blister pocket has diameter = 13.5 mm and depth = 6 mm).

Tablets were frozen into the deep freezer (REMI) at -40 ºC for 2 h. After 2 h, they were freeze-dried for 24 h using CHRIST Alpha 1-2 freeze dryer at a condenser temperature of -59 ºC and pressure 4×10^{-4} mbar. Tablets were kept into desiccators over $CaCl_2$ at room temperature until further use.

2.2.4 Characterization of FDTs

Weight Variation. Weight variation test (n = 20) for the prepared tablets was performed to check the conformity of weight. Twenty tablets were randomly picked up and their weights were determined. These weights were compared with the label claimed to calculate percentage deviation.

Hardness and Friability. Mechanical strength and friability of prepared final formulations were determined by Monsanto hardness tester and Roche friability test apparatus, respectively.

Disintegration Time. A modified disintegration apparatus method (n = 3) was used to measure the disintegration time. As per this method, we took petri dishes (10 cm diameter) and filled 10 mL distilled water to each. Prepared tablets were carefully placed in the centre of the petri dish and observed for disintegration. Time taken by tablets for complete disintegration into fine particles was noted down.

Scanning Electron Microscopy (SEM). SEM was used to study the inner structural appearance and pore size of the prepared freeze-dried tablets. Prepared tablets were sliced by a sharp knife to get the thin horizontal cross-section sample. It was then put onto a double-sided adhesive strip on an aluminium stub and micrograph was taken using an SEM (Philips XL30 ESEM TMP+ EDAX).

Solubility Studies. FXD (100 mg), prepared lyophilized formulation (F32), and a physical mixture of drug and excipients equivalent to 100 mg of the drug (PM) were taken in volumetric flasks containing a specified amount of distilled water. These solutions were shaken by vortex mixture for 15 min and followed by filtration using a membrane filter (45 µm) to get clear filtrate. The concentration of dissolved drug in the filtrate was determined by UV-visible spectrophotometer at 258 nm (n = 2).

X-ray Powder Diffraction Analysis (XRD). The samples for XRD were prepared similarly as described in Section 2.2.4.4. They were separately crushed to get the powder samples which were then placed on a sample holder of an instrument, PHILIPS, X'Pert X-ray diffractometer, simultaneously. The samples were irradiated with the monochromatized CuKα radiation and analyzed between 2 to 500 θ at 30 Kv (voltage) and 30 mA (current) to get diffractogram.

Wetting Time and Water Absorption Ratio. A study was reported on wetting time and water absorption ratio wherein a piece of double-folded tissue paper was used [26-27]. Similarly, a petri dish containing 10 mL of the water-soluble dye solution was taken and into which a tissue paper (double folded) was placed. Previously weighed tablets (Wb) were cautiously positioned on the surface of tissue paper. As soon as we kept tablets, colourful solution tried to outreach the surface of the tablet. The time needed for water to thrust out the upper surface of the tablets was known as wetting time. The moistened tablets were weighed (Wa) and the water absorption ratio, R, was calculated as follows:

$$R = [(Wa - Wb) \div Wb] \times 100 \qquad (1)$$

Mercury Porosimetry and Surface Area Analysis. Mercury porosimetry is a powerful technique used to measure the porosity, pore size, distribution, and pore volume of a material [28]. As per this method, the tablet was dried at 50-60 °C for 30-45 min and then subjected to porosimeter (THERMO QUEST, model Pascal 140 series and Pascal 440 series). Initially, the tablet was placed into a model Pascal 140 series which was then filled up with mercury. A 380 MPa pressure was applied and released slowly so that it opened up the bigger sized pores. Then the tablet was loaded into Pascal 440 series, filled up with mercury and 380 MPa pressure was applied to cover the smaller pores. Finally, the pressure was released slowly to reach a normal condition. By combining these data, pore size

distribution was generated.

The Lyophilized Tablet Index. The lyophilized tablet index (LTI) was developed by Al Husban et al. [29-30], which helps to quantify the enhancement of tablet properties occurring due to changes made in tablet formulation. As per this method, tablet hardness and disintegration time were compared as follows:

$$LTI = (H \div DT) \div (H^{\circ} \div DT^{\circ}) \quad (2)$$

where,

H: hardness of prepared tablet (kg/cm^2);

DT: disintegration time of prepared tablet (s);

H^{o}: hardness of the control tablets (1.5 kg/cm^2);

DT^{o}: disintegration time of the control tablet (6 s).

An improvement in tablet properties is inferred if an LTI > 1.

***In Vitro* Drug Release Studies.** Dissolution characterization of prepared FDTs was performed by United States Pharmacopoeia (USP) paddle instrument. The testing was carried out using 500 mL of phosphate buffer (pH 6.8) as dissolution media, kept at 37 ± 0.5 °C under 50 rpm. Five mL aliquots were collected at 0, 1, 2, 3, 4, 5 min time intervals by maintaining the sink conditions and subjected to filtration using a membrane filter (0.45 µm). The filtrate was assayed spectrophotometrically at 258 nm to quantify the amount of drug released. The comparison was made between the *in vitro* dissolution profile of prepared lyophilized tablets of FXD and the conventional market formulation (Allegra TM 60 mg oral tablets).

Stability Studies. The International Conference on Harmonization (ICH) guidelines for zone III and IV were used to perform stability studies of prepared tablets. As per these guidelines, tablets were stored at 25 ± 2 °C/60 ± 5% and 40 ± 2 °C/75 ± 5% RH for one month in a stability chamber (Thermo Lab, Mumbai). The tablets were withdrawn at 15 days' time intervals and were evaluated for visual defects, hardness, disintegration and drug content.

3. Results and Discussion

3.1 Identification of FXD

3.1.1 Melting Point Determination

The melting point of FXD was found to be 199-201 °C, which is in agreement with the standard melting point of FXD (200-204 °C).

3.1.2 FTIR Spectra of Drug

The major peaks obtained in the infra-red spectra of the drug are shown in Fig. 1 and tabulated in Table 1. According to assigned functional groups in the

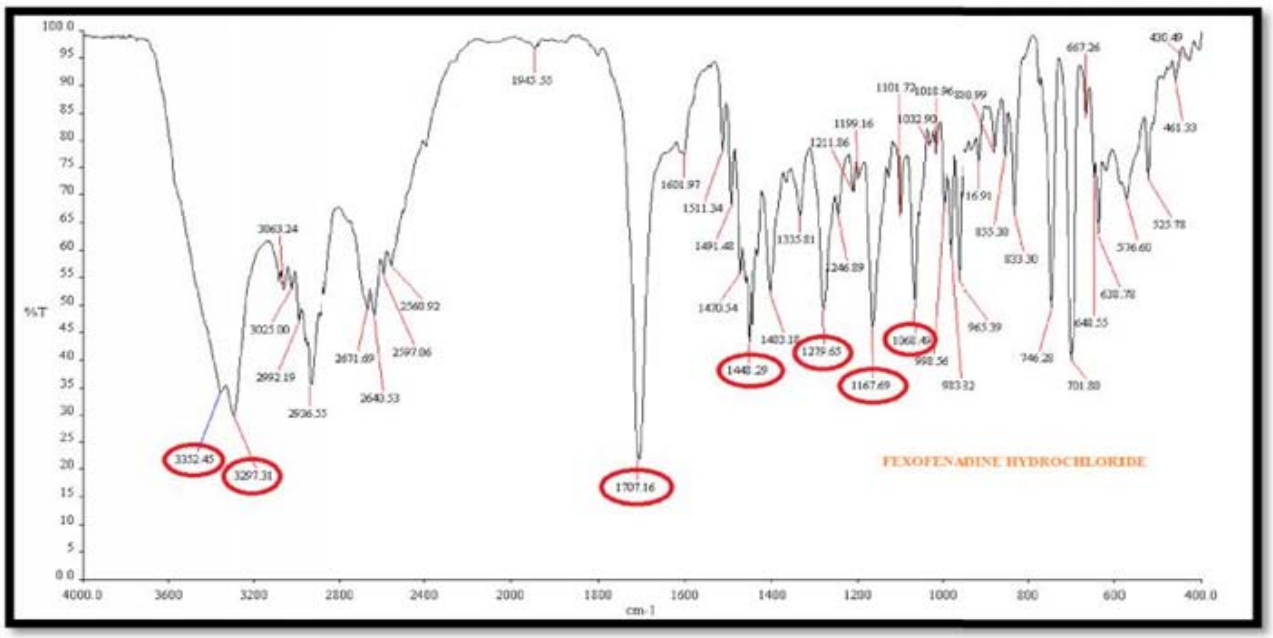

Fig. 1 FTIR spectra of FXD.

Table 1 FTIR frequencies of fexofenadine HCl.

Functional groups	Observed frequency
Aliphatic (O-H stretch)	3,297 cm^{-1}, 3,352 cm^{-1}
Carbonyl group (C = 0 stretch)	1,705 cm^{-1}
3º alcohol (0-H stretch)	1,403 cm^{-1}
C-N stretch of 3º amine	1,279 cm^{-1}
C-0 stretch of 3º alcohol	1,167 cm^{-1}
C-0 stretch of 2º alcohol	1,068 cm^{-1}

molecular structure of FXD, the relevant peaks were obtained (Table 1). No other non-relevant peaks were obtained. So, it can be concluded that the given drug sample is pure.

3.2 Drug-Excipient Studies

The DSC thermograms of FXD and PM are depicted in Fig. 2. A sharp peak at 203.171 °C in pure drug and 202.949 °C in PM recorded which might be due to its melting point. DSC thermograms of FXD and PM are almost superimposed which inferred that there were no considerable changes in melting endotherm. Thus, we can predict no incompatibility between the drug and the excipients used in the following formulation.

3.3 Preparation and Characterization of FDTs Containing FXD by Lyophilization Method

3.3.1 Trial Formulations

Trial formulations (F1-F26) containing gelatin/maltodextrin/acacia with a varying concentration of glycine (matrix-forming agent) along with mannitol (to impart crystallinity and elegance effect) were prepared as per Tables 2 and 3. Physical appearance, mechanical strength (manually) and disintegration time (DT) were considered for optimization of the concentration of binders and glycine. Results for these formulations are shown in Figs. 3 and 4. Tablets (F1-F12) were found to undergone shrinkage with distorted shapes. Their hardness was also seemed to be poor brittle during handling. It was also observed that with increased concentration gelatin, DT was also increased (which is not desirable) and hence, 3.5% *w*/*v* gelatin was selected for further studies. To avoid shrinkage problem, two formulations (F13-F14) were prepared using 30% *w*/*w* and 40% *w*/*w* concentration of glycine. Tablets containing 30% *w*/*w* of glycine had a promising fast disintegration with good shape and hardness compared to 40% *w*/*w* glycine. Formulations (F15-F26) were prepared and evaluated based on the physical appearance, DT and mechanical strength. Tablets containing maltodextrin (10 and 20% *w*/*v*) and acacia (10 and 15% *w*/*v*) with 30% *w*/*w* glycine of total solids had desirable hardness with fast disintegration. Further detailed evaluation was done for these combinations.

3.3.2 Final Formulations

Final formulations (F27-F32) were prepared with 30% *w*/*w* of glycine and a selected concentration of gelatin, maltodextrin, and acacia as shown in Table 4. Hardness, friability, weight variation, DT and drug content were found out for these formulations and represented in Table 5. Photographs of these formulations are presented in Fig. 5, which indicated that they have relatively good shapes and textured surfaces. Selection of better batch was done based on hardness and DT. As per these criteria, F32 was found promising due to its minimum DT (3.33 s) and relatively high mechanical strength (1.833 kg/cm^2). Hence, it was studied further as follows.

Scanning Electron Microscopy. The inner structure of the lyophilized tablets was observed by SEM. SEM photomicrograph offers a great opportunity for direct assessment internal structure that helps in comparing prepared tablets based on surface morphology. Fig. 6 shows SEM photomicrographs of formulations F27, F29 and F32. SEM results showed that F32 has got highly porous structure than F29 and F27 that might facilitate rapid penetration of dissolution

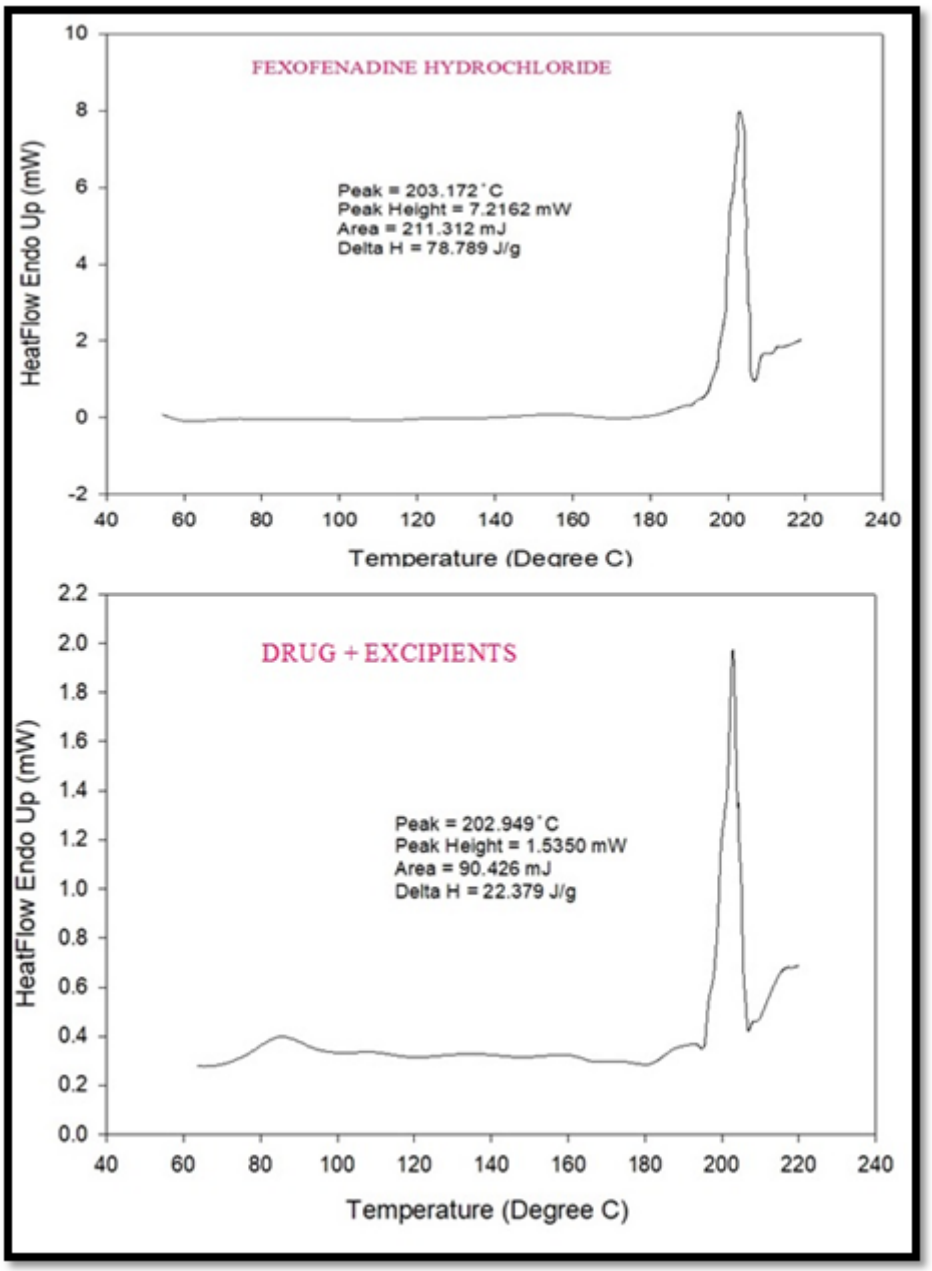

Fig. 2 Drug excipients compatibility studies by DSC.

medium into a tablet to trigger fast drug release.

Solubility Studies in Distilled Water. As per solubility studies, the order of solubility of FXD was found to be FDTs (0.197 mg/mL) > PM (0.055 mg/mL) > pure drug (0.026 mg/mL). The solubility of the drug in prepared tablets was 8 times higher than the pure drug and 3.5 times higher than PM. This drastic increase in FXD solubility in the formulation might be attributed to a high amount of an amorphous form of FXD generated due to lyophilization, utilization of highly water-soluble carrier materials along with glycine, increased surface area and wettability that all together could synergize the overall solubilizing effect.

X-ray Powder Diffraction Analysis. To evaluate the solubility characteristics of optimized formulation, XRD was done for pure FXD, PM and prepared FDTs (F32). Fig. 7 shows the XRD of the stated samples. The pure FXD exhibited its characteristic diffraction peaks

Table 2 Preliminary formulations containing gelatin (F1-F14).

Formulations	Ingredients	
	Gelatin (% *w*/*v*)	Glycine (% *w*/*w* of total solids)
F1	2	5
F2	2	10
F3	2	15
F4	3.5	5
F5	3.5	10
F6	3.5	15
F7	5	5
F8	5	10
F9	5	20
F10	7	5
F11	7	10
F12	7	20
F13	3.5	30
F14	3.5	40

Each tablet containing FXD (60 mg), mannitol (10% *w*/*w* of total solids) and distilled water quantity sufficient to 1 mL.

Table 3 Preliminary formulations containing maltodextrin and acacia (F15-F26).

Formulations	Ingredients		
	Maltodextrin (% *w*/*v*)	Glycine (% *w*/*v* of total solids)	Acacia (% *w*/*v*)
F15	5	15	-
F16	10	30	-
F17	20	15	-
F18	5	30	-
F19	10	15	-
F20	20	30	-
F21	-	30	5
F22	-	40	10
F23	-	30	15
F24	-	40	5
F25	-	30	10
F26	-	40	15

Each tablet containing FXD (60 mg), mannitol (10% *w*/*w* of total solids) and distilled water quantity sufficient to 1 mL.

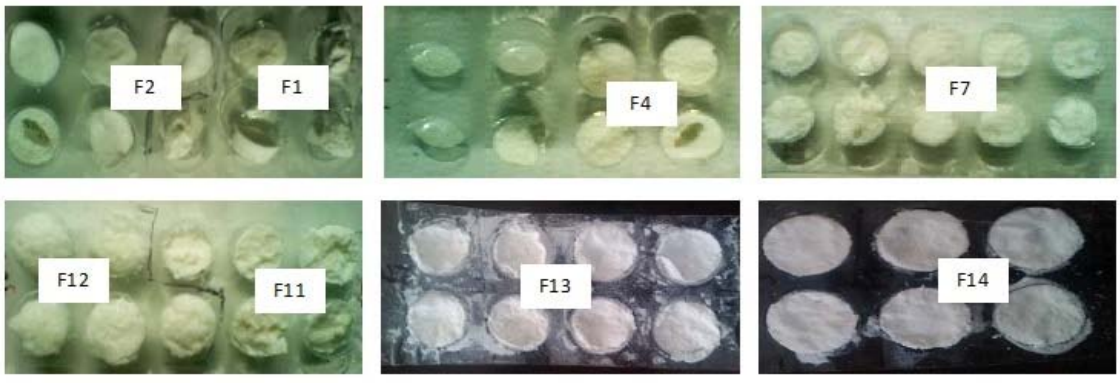

Fig. 3 Photographs of trial batches.

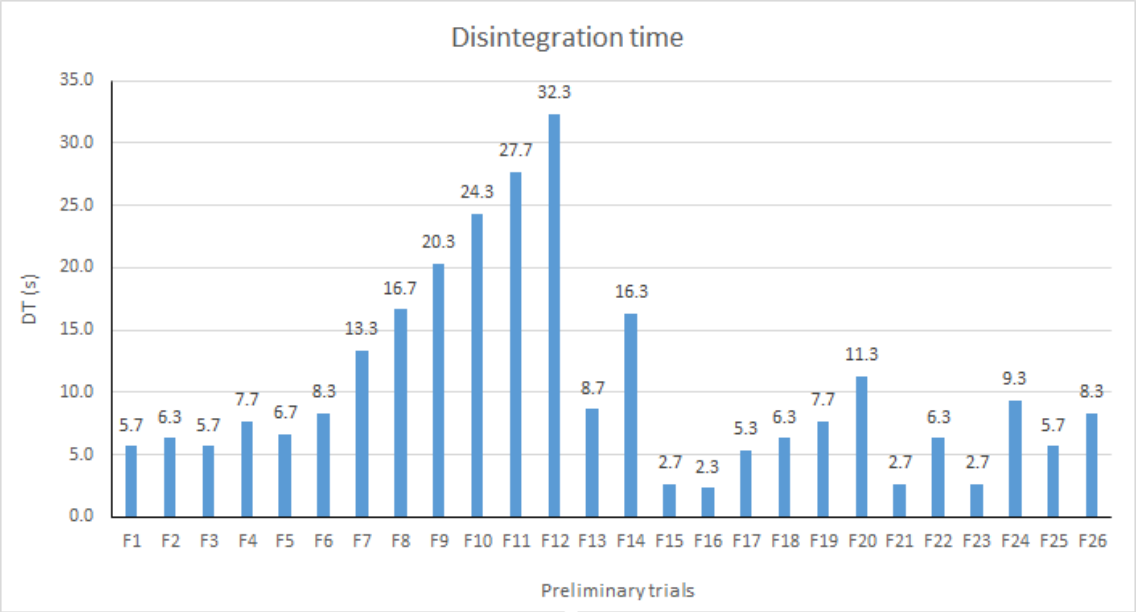

Fig. 4 Disintegration time of trial batches.

Table 4 Final formulations containing gelatin, maltodextrin and acacia.

Ingredients	Final formulations					
	F27	F28	F29	F30	F31	F32
Gelatin (% *w*/*v*)	3.5	5	-	-	-	-
Maltodextrin (% *w*/*v*)	-	-	10	20	-	-
Acacia (% *w*/*v*)	-	-	-	-	10	15

Each tablet containing FXD (60 mg), glycine (30% *w*/*w* of total solids), mannitol (10% *w*/*w* of total solids) and distilled water quantity sufficient to 1 mL.

Table 5 Evaluation of prepared formulations (F27-F32).

Formulations	Hardness (kg/cm^2)	Friability (%)	Weight variation (mg ± SD)	Disintegration time (s ± SD)	Drug content (% ± SD)
F27	1.5 ± 0.5	0.35	181.81 ± 2.08	7.67 ± 0.47	92.59 ± 2.5
F28	1.83 ± 0.28	0.31	258.18 ± 1.72	13.33 ± 1.24	98.14 ± 2.3
F29	0.67 ± 0.31	4.21	235.09 ± 3.56	3.66 ± 0.47	89.81 ± 1.6
F30	1.17 ± 0.24	1.71	334.90 ± 1.12	4.67 ± 0.61	91.85 ± 1.9
F31	1.17 ± 0.34	0.58	234.36 ± 2.50	3.33 ± 0.44	98.14 ± 2.2
F32	1.33 ± 0.28	0.35	283.63 ± 2.37	3.33 ± 0.54	97.78 ± 0.9

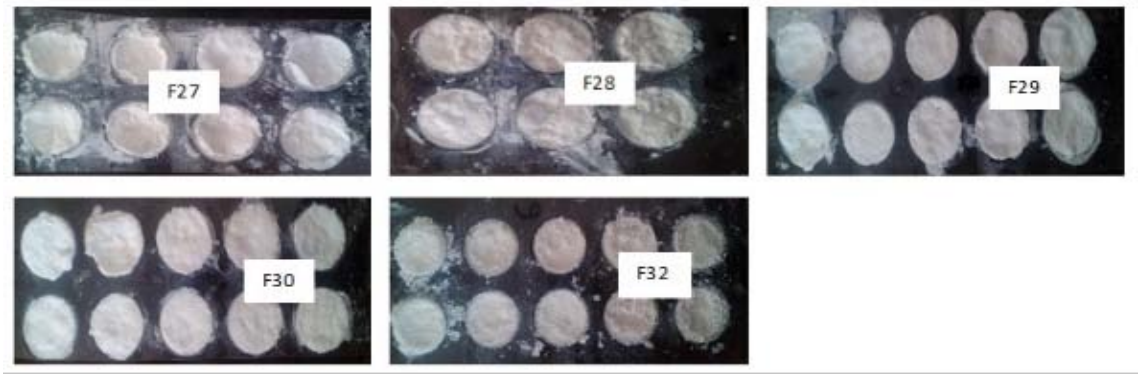

Fig. 5 Photographs of final batches.

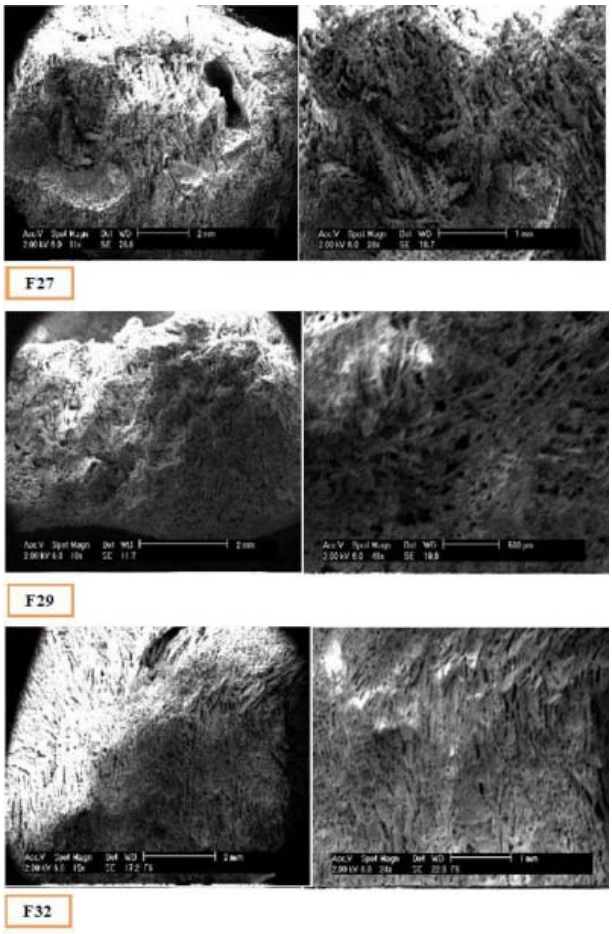

Fig. 6 SEM of lyophilized tablets formulation (F27, F29 and F32) at low and high resolution.

at various diffraction angles, thus indicating the presence of crystallinity. The sharp peaks for FXD at 2° theta 14.05°, 17.5°, 18.22°, 19.3°, 19.84°, and 22.88° have indicated crystallinity of the drug. Lyophilized tablet showed decreased peak number and intensity in comparison with pure FXD in which the FXD peak number decreased from 25° to 8°, and peaks at 14.05°, 18.22°, 19.3°, and 22.88° had been disappeared. The XRD pattern of the PM showed the similar peaks like that of pure FXD that suggested the crystalline drug molecules still present in the mixture, although their intensity was lower due to the high excipients-drug ratio employed. The diffraction pattern of the lyophilized tablet showed either non-existence or broadening or depletion in some major FXD diffraction peaks, thus it indicated that a reduction in crystallinity and contained mostly an amorphous form in the lyophilized tablet. These outcomes could describe the observed enhancement of solubility and rapid dissolution of FXD in lyophilized FDTs.

Wetting Time and Water Absorption Ratio. Fig. 8 shows photographs of wetting time for F27-F32. Wetting time was calculated in seconds and it was found to be F27 (15 s), F28 (18 s), F29 (7 s), F30 (8 s), F31 (7 s), and F32 (7 s). The water absorption ratio (%) was found to be increased from F27 (48.28) < F28 (59.12) < F29 (69.53) < F30 (75.94) < F31 (76.81) < F32 (80.22). The lower value of wetting time and higher value of water absorption ratio were observed for F32 formulation. This may be due to the highly porous structure and good capillary action observed for such formulation containing acacia.

Mercury Porosimetry Studies and Surface Area Analysis. Mercury porosimetry study was employed to furnish particulars on bulk density and porous microstructure of pervious lyophilized tablets, to put

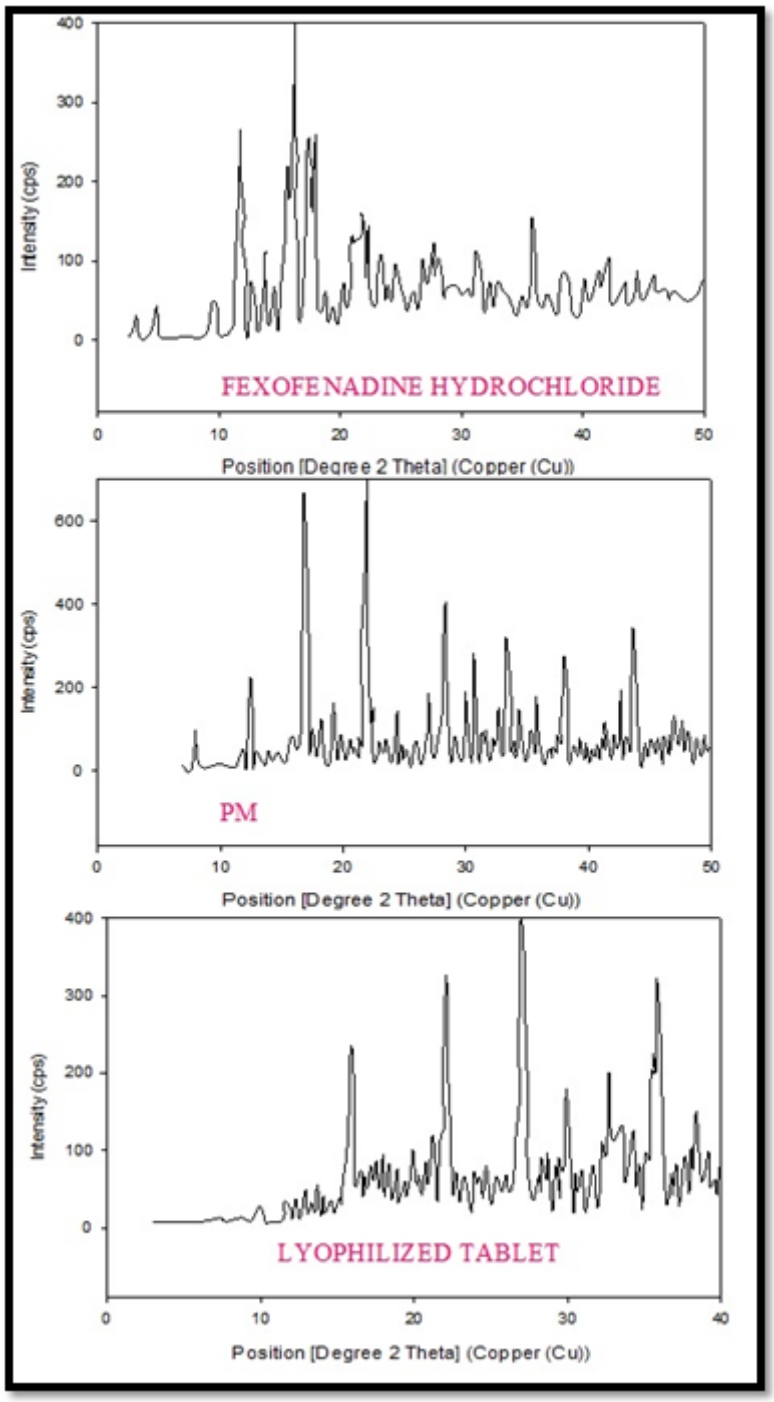

Fig. 7 XRPD pattern of pure drug, physical mixture (PM) and lyophilized tablet formulation (F32).

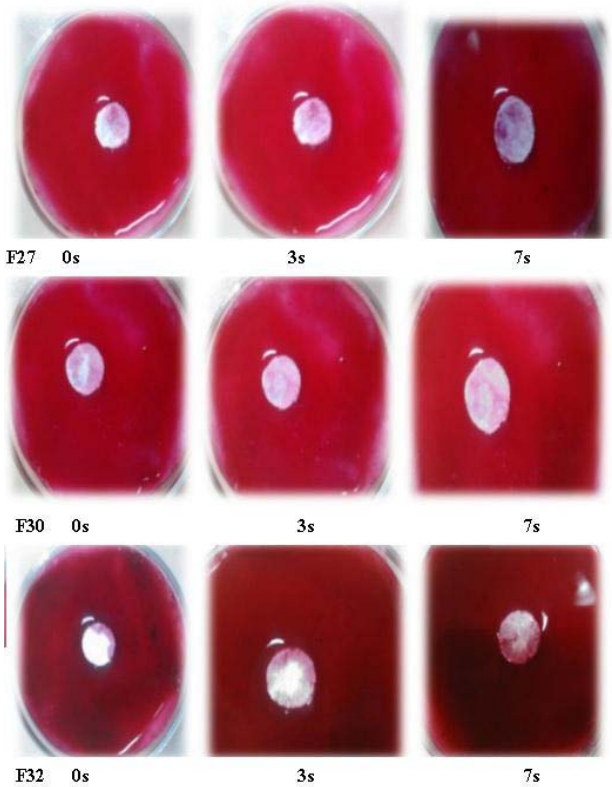

Fig. 8 Photographs of wetting time of the lyophilized tablet formulations (F27-F32).

forward a means for fast dissolution/disintegration of lyophilized tablets. Hence, it was performed for our optimized formulation (F32) and simultaneously surface area analysis was also done. It was found that lyophilized tablet has a surface area of 4.974 m^2/g and total porosity of 23.2784% which might be responsible for faster disintegration of the tablets. Other parameters viz. total cumulative volume (0.5867 cc/g), average pore diameter (4.406846 µ), bulk density (0.39677 g/cm^3), apparent density (0.51715 g/cm^3) and sample volume correlation (0.9706193) were also calculated that had imparted physical nature of prepared formulation (F32).

The Lyophilized Tablet Index. The concept of LTI assures a higher value for the favourable enhancement in hardness and disintegration time. Additionally, it can be employed to order such augmentation in tablet properties among prepared formulations. It was found to be 0.7988 (F27), 0.56167 (F28), 0.74438 (F29), 1.02072 (F30), 1.43146 (F31) and 1.63507 (F32). Acacia containing formulation (F32) achieved the highest value that inferred favourable overall tablet properties.

***In Vitro* Dissolution Study.** The dissolution study was carried out for the FDTs (F37-F32) to obtain the percentage drug release within 5 min. Fig. 9 shows that the FXD got completely dissolved within a few minutes of the study. This was attributed to the fast-dissolving nature of prepared lyophilized tablets which was supported by the above-performed studies.

Stability Studies. The favourable formulation (F32) was subjected to short term stability studies by storing at 25 ± 2 °C/60 ± 5% and to accelerated stability studies by storing at 40 ± 2 °C/75 ± 5% RH for one month. After one month, tablets were examined for the visual defects, mechanical strength, drug content and disintegration time. Table 6 shows the characteristics of the prepared FTDs post stability studies. There was no significant change in appearance, hardness, drug content and disintegration time which was observed at 25 ± 2 °C/60 ± 5% RH conditions suggesting that the formulation was stable. However, a significant change

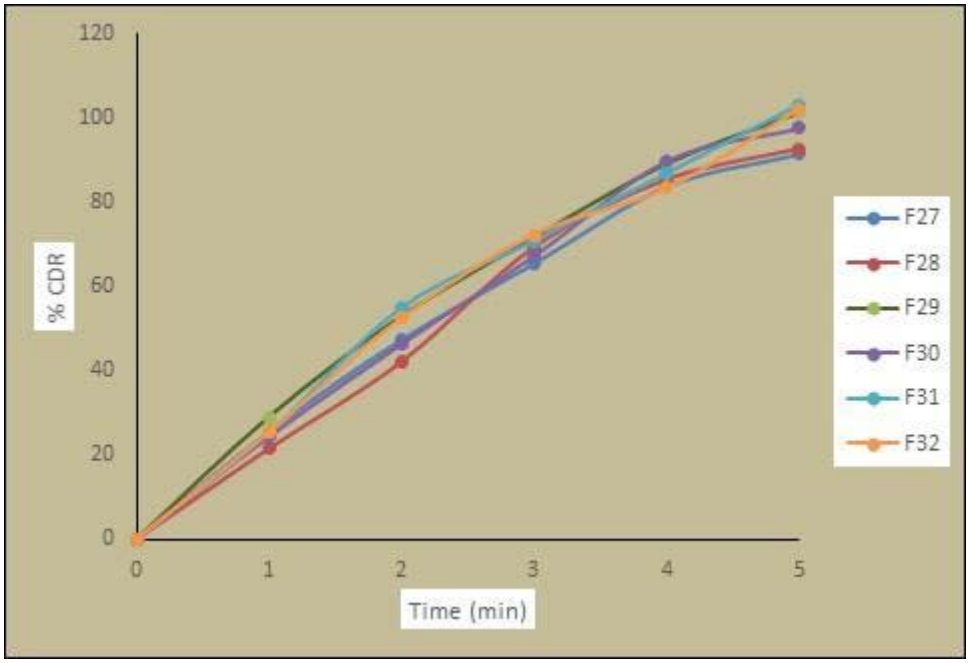

Fig. 9 ***In-vitro*** **dissolution profile of lyophilized tablet formulations (F27-F32).**

Table 6 Stability studies for the lyophilized formulation (F32).

Time		Visual defects	Hardness (kg/cm^2)	Drug content (%)	DT (s)
0 d	25 °C/60% RH	No change	1.3	97.78	3.3
	40 °C/75% RH	No change	1.3	97.78	3.3
15 d	25 °C/60% RH	No change	1.3	97.94	3.3
	40 °C/75% RH	Slight shrinkage	1.0	96.91	2.8
30 d	25 °C/60% RH	No change	1.2	97.51	3.3
	40 °C/75% RH	Shrinkage and breakage	-	-	-

in appearance, hardness, drug content and disintegration time was observed at 40 °C/75% RH conditions which indicated that the prepared formulation was unstable at higher temperature and humidity.

4. Conclusions

FDTs containing FXD have been developed by lyophilization method using different water-soluble polymers along with glycine and mannitol. The tablets prepared by combination of acacia and higher concentration glycine were found to have favourable physical and chemical properties. Pre-compression and post-compression parameters of prepared FDTs were found to be within the desirable limits. Formulation (F32) resulted in a significant improvement in the drug dissolution, which can be explored further to correlate with its oral bioavailability enhancement.

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