

FORMULATION AND EVALUATION OF FAST DISSOLVING FILMS OF ELETRIPTAN HYDROBROMIDE

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ABSTRACT

Objective: The main aim of the present research was to develop an oral fast dissolving polymeric film (FDF) with good mechanical properties, faster disintegration and dissolution when placed on the tongue.

Methods: Eletriptan hydrobromide is prescribed for the treatment of mild to a moderate migraine. The polymers selected for preparing films were Pullulan, Maltodextrin (MDX), Acacia, Sodium alginate (SA), Locust bean gum (LBG), Guar gum (GG), Xanthan gum (XG), Polyvinyl alcohol (PVA), Polyvinyl pyrrolidone (PVP), Hydroxyl propyl methyl cellulose (HPMC) E5, and HPMC E15. Twelve sets of films FN1-FN12 were prepared by solvent casting method with Pullulan and combination of Acacia, MDX, SA, LBG, GG, XG, PVA, PVP, HPMC E5 and HPMC E15. Five sets of films FS1-FS5 were prepared using synthetic polymers like PVA, PVP, HPMC E5 and HPMC E15.

Results: From all the prepared polymer formulations, FN2, FN8, and FS3 were selected based on disintegration time, and drug release and amongst this three FN2 was optimised based on its disintegration time (D. T). The percent drug release of the optimised film was compared with the percent release of the pure drug.

Conclusion: The optimised formulation had a D. T of 16 s and a percent drug release of 97.5% in 10 min in pH 6.8 phosphate buffer and 100.6% drug release in 10 min in 0.1N HCl.

Keywords: oral FDFs, Pediatric, Geriatric, Dysphasia

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INTRODUCTION

The oral route is one of the oldest routes which is used for conventional and novel drug delivery. The main reason for this route being the highly preferred is ease of administration. FDFs, a new drug delivery system for the oral delivery of the drugs, was developed in late 1970's based on the technology of the transdermal patch. These were developed as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties in swallowing traditional oral solid-dosage forms [1]. By definition, "a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for administration of water is known as an oral fast-dispersing dosage form"[2].

The novel technologies of oral fast-dispersing dosage forms are also known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating systems. However, the function and concept of all these dosage forms are similar. These fast dissolving systems are used in the condition called Dysphasia (difficulty in swallowing), this is common among all age groups but especially in geriatric and pediatric patients [3].

Special features of FDFs [4, 5]

- Thin, elegant film
- Available in various sizes and shapes
- Unobstructive
- Excellent mucoadhesion
- Fast disintegration
- Rapid release

Advantages of oral FDFs [6-9]

- Rapid onset of action and increased bioavailability.

- Suitability for old patients, who experience difficulties in swallowing, mentally ill, the developmentally disable and the patients who are uncooperative, or are on reduced liquid intake plans or are nauseated.
- Avoidance of water facilitating to use even in travelling.
- Rapid disintegration than oral disintegrating tablet due to larger surface area.
- Beneficial in cases such as motion sickness, acute pain, episodes of allergic attack or coughing, where an ultra-rapid onset of action required.
- The oral or buccal mucosa being highly vascularised, drugs can be absorbed directly and can enter the systemic circulation without undergoing first pass hepatic metabolism. This advantage can be exploited in preparing products with the improved oral bioavailability of molecules that undergo first pass effect.
- The risk of choking or suffocation during oral administration of conventional formulation due to physical obstruction is avoided, thus providing improved safety.
- The sublingual and buccal delivery of a drug via thin film has the potential to improve the onset of action, lower the dosing, and enhance the efficacy and safety profile of the medicament.
- Delivery can also be terminated easily if required.

Disadvantages of oral FDFs [10, 11]

- Drugs which are unstable at buccal pH cannot be administered.
- Drugs which irritate the mucosa cannot be administered by this route.
- Drug with small dose requirement can only be administered.
- Most of the drugs are bitter in taste needs taste masking.

- FDF's are fragile and must be protected from water, so it needs special packaging.

MATERIALS AND METHODS

Eletriptan hydrobromide was used as an active ingredient, acacia, maltodextrin, sodium alginate, locust bean gum, xanthan gum, guar gum, HPMC E5, E15, PVA, PVP were used as water soluble polymers. Mannitol used as a sweetening agent and propylene glycol as a plasticizer. All polymers, propylene glycol, Mannitol and Glycerol, were procured from SD Fine chemicals Ltd. All other chemicals used were of analytical grade.

Formulation of FDFs

The general methods used to prepare FDFs are semisolid casting, solvent casting, hot melt extrusion, solid dispersion and rolling. In the present study, the FDF's were prepared using solvent casting method [10]. The casting solution was prepared by mixing polymer solution with drug, plasticizer, sweetener and flavor. The resulting solution was deaerated by sonication, then poured into appropriate moulds and dried to obtain the films. The final dosage form was cut into strips

(2×2 cm) which contained the required amount of drug (20 mg). Different formulations were prepared by varying the polymers and plasticizer concentrations (table 1 and 2). The prepared films were then evaluated for thickness, folding endurance, weight variation, disintegration time, dissolution time and drug content.

Evaluation of films

Standard curve of eletriptan hydrobromide

The standard curve of EHBR was obtained in two different mediums 6.8 pH phosphate buffer and 0.1N HCl. 100 mg of EHBR was dissolved in 10 ml of 6.8 pH phosphate buffer and another 100 mg of drug was dissolved in 0.1N HCl, then the volume was made up to 100 ml with respective mediums. 10 ml of the above solutions were diluted up to 100 ml with buffer and 0.1N HCl respectively. From this solution, 1 ml was taken, and volume was made up to 100 ml (1 µg/ml). Then by serial dilution, solutions with concentrations 2 µg/ml, 4 µg/ml, 6 µg/ml, 8 µg/ml, 10 µg/ml, 12 µg/ml, 14 µg/ml and 16 µg/ml were prepared. Absorbance was measured on a Shimadzu Double Beam Spectrophotometer (UV1601) at 222.0 nm (table 3, 4).

Table 1: Composition of different films made of natural polymers

Ingredients	FN1	FN2	FN3	FN4	FN5	FN6	FN7	FN8	FN9	FN 10	FN 11	FN 12
EHBR	140	140	140	140	140	140	140	140	140	140	140	140
PULLULAN*	2	2	2	2	2	2	2	2	2	2	2	2
ACACIA*	0.5	-	-	-	-	-	1	-	-	-	-	-
MALTO-DEXTRIN*	-	1	-	-	-	-	-	2	-	-	-	-
LOCUST BEANGUM*	-	-	0.5	-	-	-	-	-	1	-	-	-
SODIUM ALGINATE*	-	-	-	0.5	-	-	-	-	-	1	-	-
GUAR GUM*	-	-	-	-	.25	-	-	-	-	-	.50	-
XANTHAN GUM*	-	-	-	-	-	0.5	-	-	-	-	-	.75
MANNITOL*	20	20	20	20	20	20	20	20	20	20	20	20
PROPYLENEGLYCOL**	10	10	10	10	10	10	10	10	10	10	10	10
WATER	10	10	10	10	10	10	10	10	10	10	10	10

NOTE: All the ingredients were dissolved in 10 ml distilled water, EHBR-Eletriptan hydrobromide in mg; FN-Formulations with natural polymers, *are in %w/v; **is in % w/w of the polymer.

Table 2: Preparation of oral films using combination of various synthetic polymers

Ingredients	FS1	FS2	FS3	FS4	FS5
EHBR	140	140	140	140	140
PVA*	3	1.75	-	-	-
PVP*	2	-	-	-	2
HPMC E5*	-	1.75	3	1	3
HPMC E15*	-	-	-	2	-
Mannitol*	0.2	0.2	0.2	0.2	0.2
Propylene glycol**	-	0.2	0.5	-	0.2
PEG 400*	0.2	-	-	0.3	-
Water	10	10	10	10	10

*-are in %w/v; ** is in % w/w of polymer.

Table 3: Standard graph of EHBR in pH 6.8 Phosphate buffer

Concn (ug/ml)	Absorbance (mean±SD)
0	0
2	0.178±0.0027
4	0.348±0.015
6	0.503±0.013
8	0.684±0.027
10	0.829±0.036
12	0.981±0.024
14	1.144±0.0051

n=6

Drug-excipients compatibility study by FT-IR

EHBR compatibility with excipients was studied by FT-IR spectroscopy. From the spectra of the EHBR, it was observed

that the main functional groups of the molecule were aromatic phenyl with sulfone and amide. The most intensive peak was observed at 1140 cm⁻¹ which were due to C-N bending in the structure of EHBR. Another sharp peak was seen at 1640 cm⁻¹

which indicated the presence of C=C (phenyl group), peak at 1305 cm⁻¹ was due to sulfone moiety. A peak at 3245 cm⁻¹ indicated the presence of N-H stretch, N-H bending was seen at 1480 cm⁻¹, and a peak at 528 cm⁻¹ was due to the presence of bromide group as seen in fig. 3.

From the FTIR spectra as seen in fig 4, it is very clear that the drug is compatible with pullulan and Maltodextrin as all the characteristic peaks of drug were retained. Hence there is no incompatibility between the drug and these excipients.

Table 4: Standard graph of EHBR in 0.1N HCl

Concn (ug/ml)	Absorbance (mean±SD)
0	0
2	0.210±0.0061
4	0.357±0.0092
6	0.512±0.0115
8	0.652±0.0030
10	0.828±0.0035
12	0.98±0.001
14	1.15±0.002

n=6

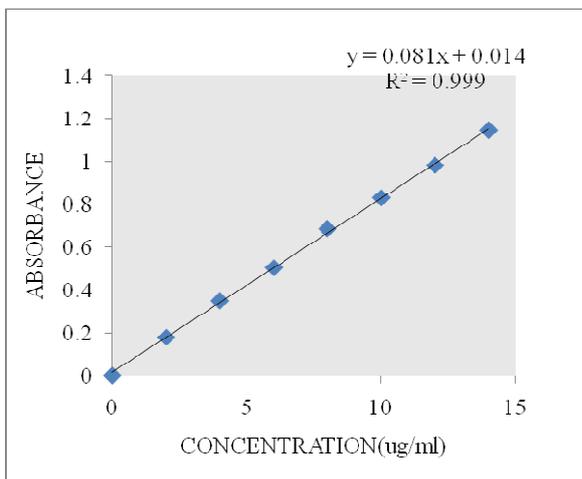


Fig. 1: Standard graph of EHBR in pH 6.8 phosphate buffer

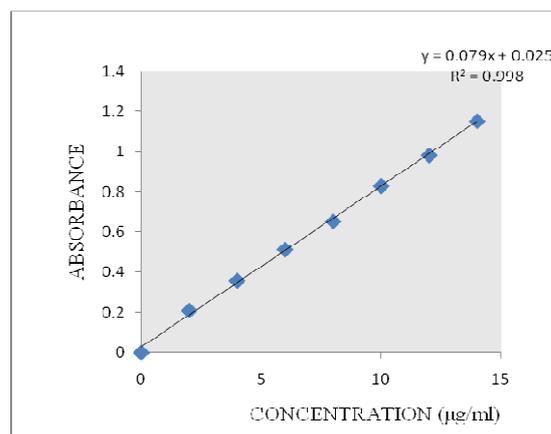


Fig. 2: Standard graph of EHBR in 0.1N HCl

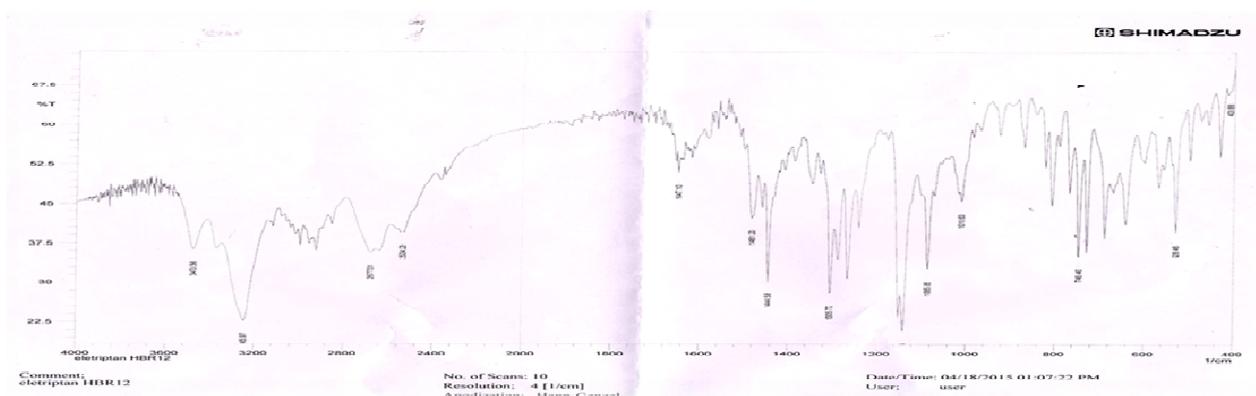


Fig. 3: FTIR spectrum of pure drug

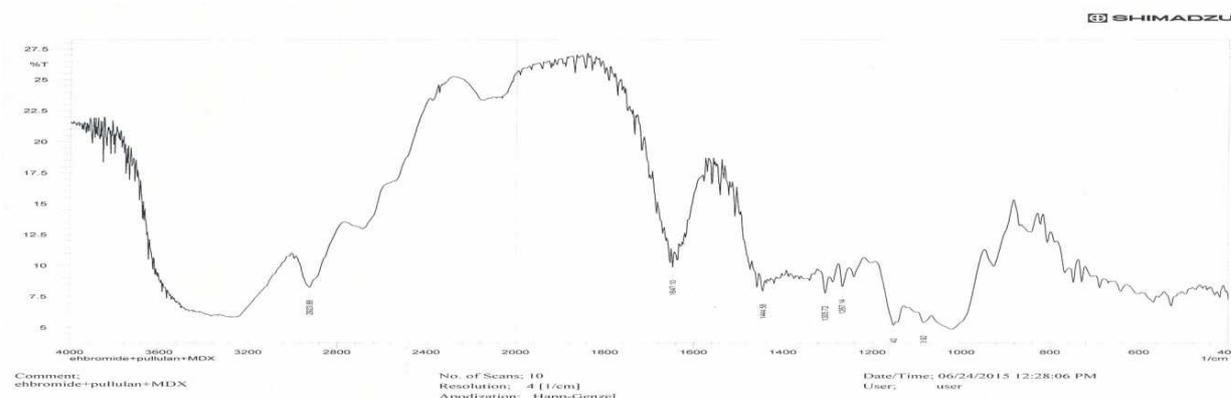


Fig. 4: FTIR spectrum of EHBR, pullulan and maltodextrin

Weight variation of the film

The casted film was cut into various 2x2 cm films from different locations. The weight of each film strip was taken and the weight variation was calculated.

Thickness of the film

The thickness of the film was measured by using screw gauge at various points of film and the average thickness was calculated.

Folding endurance

The folding endurance is expressed as the number of folds required for developing visible cracks or breaking any given film. This gives

an indication of brittleness or flexibility of the film. A 2x2 cm strip was subjected to this test by folding the film at the same point repeatedly several times until a visible crack was observed.

Disintegration time

Disintegration time study was slightly modified to mimic the *in vitro* and *in vivo* conditions. For the study, 2 x2 cm film required for dose delivery was placed in a petri plate with 5 ml of pH 6.8 phosphate buffer. The time taken for the disintegration of the film was measured as the disintegration time. This test was followed in the present study, evaluation was done in triplicates and the standard deviation from the mean value was reported time required for the film to break and disintegrate was noted as *in vitro* disintegration time.

Table 5: Evaluation of FDFs prepared with natural polymers

Formulation code	Weight variation (mg)	Folding endurance	Content uniformity (mg)	Assay (%)	Thickness (μ g)	Disintegration time (s)
FN1	64.66 \pm 0.577	155	19.88 \pm 0.090	97.4	72 \pm 4.47	21.33 \pm 0.577
FN2	78.33 \pm 0.577	160	19.94 \pm 0.069	99.8	76 \pm 5.47	15.66 \pm 0.577
FN3	61.33 \pm 0.577	160	19.85 \pm 0.143	97.0	74 \pm 5.47	34 \pm 1.00
FN4	67.66 \pm 0.577	155	19.84 \pm 0.126	96.8	68 \pm 4.47	48 \pm 1.00
FN5	65.66 \pm 0.577	150	19.61 \pm 0.529	97.6	56 \pm 5.47	31.66 \pm 0.577
FN6	62.33 \pm 0.577	150	19.81 \pm 0.13	96.2	64 \pm 5.47	58 \pm 1.00
FN7	74.33 \pm 0.577	160	19.94 \pm 0.030	99.6	116 \pm 5.47	26.33 \pm 0.577
FN8	87.33 \pm 1.15	165	19.50 \pm 0.470	97.3	84 \pm 5.47	17.66 \pm 0.577
FN9	73.33 \pm 0.577	160	19.90 \pm 0.030	95.4	92 \pm 4.47	37.33 \pm 0.577
FN10	71.66 \pm 0.577	155	19.80 \pm 0.145	96.3	94 \pm 5.47	53.33 \pm 0.577
FN11	70.66 \pm 1.15	165	19.61 \pm 0.491	97.2	77 \pm 4.47	31.66 \pm 1.577
FN12	68.33 \pm 1.15	160	19.79 \pm 0.080	96.5	88 \pm 2.73	59.33 \pm 0.577

Table 6: Evaluation of FDFs prepared with synthetic polymers

Formulation code	Weight variation (mg)	Folding endurance	Content uniformity (mg)	Assay (%)	Thickness (μ g)	Disintegration time (s)
FS1	128.33 \pm 0.577	150	18.88 \pm 0.090	96.2	104 \pm 5.47	49.33 \pm 0.577
FS2	97.33 \pm 1.154	150	19.12 \pm 0.140	97.0	88 \pm 4.47	56.33 \pm 0.577
FS3	92.66 \pm 0.577	160	19.64 \pm 0.045	99.7	84 \pm 4.47	37.66 \pm 0.577
FS4	89.66 \pm 0.577	150	19.0 \pm 0.025	97.5	78 \pm 8.94	40.66 \pm 0.577
FS5	120.66 \pm 0.577	155	19.16 \pm 0.056	95.2	94 \pm 4.47	59.66 \pm 1.15

In vitro dissolution studies

The *in vitro* dissolution studies were conducted using 0.1N HCl and pH 6.8 phosphate buffer (900 ml). The dissolution studies were carried out using six basket dissolution apparatus at 37 \pm 0.5 °C and at 50 rpm. Each 2 x 2 cm film was submerged into dissolution media. Samples were withdrawn at 1, 3, 5, 10, 15 and

30 min time intervals and filtered through Whatman filter paper and were analyzed spectrophotometrically at 222 nm. To maintain the volume, an equal volume of fresh dissolution medium maintained at same temperature was added after withdrawing samples. The absorbance values were converted to concentration using standard calibration curve previously obtained from the study.

Table 7: Dissolution data of the optimized formulation in 6.8 pH phosphate buffer

Time (min)	% drug release
0	0
1	30.0
3	73.0
5	86.5
10	97.5
15	109.3

Table 8: Dissolution data of the optimized formulation in 0.1N HCl

Time (min)	% drug release
0	0
1	64.0
3	76.8
5	91.8
10	100.66
15	-

RESULTS AND DISCUSSION

In the present study, each FDF of 2x2 cm in size contained 20 mg of Eletriptan hydrobromide. The films were prepared using natural and synthetic polymers, amongst which the films of natural polymers disintegrated faster than the films of synthetic polymers. The films dissolved completely within one minute. The prepared films were tested for various parameters weight variation, thickness, folding endurance, disintegration and dissolution results are showed in table 5. FN2 was chosen as optimized formulation as it had a shortest D. T of 16 s. The dissolution studies were carried out in 6.8 pH phosphate buffer and 0.1N HCl, FN2 showed a percentage release of upto 100% within 10 min in both mediums.

A comparative study of drug release of optimized formulation and the pure drug was done in 6.8 pH phosphate buffer, and 0.1N HCl which showed the optimized formulation FN2 showed a faster drug release than pure drug as in fig. no 5 and 6.

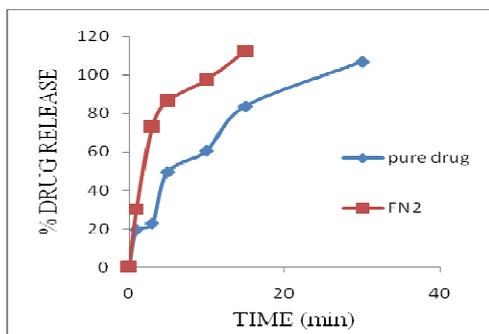


Fig. 5: Comparison of dissolution profiles of optimized film and pure drug EHBR in 6.8 pH phosphate buffer

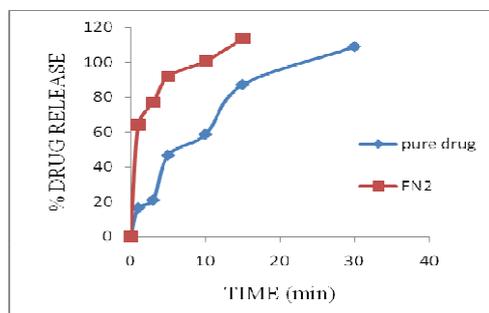


Fig. 6: Comparison of dissolution profiles of optimized film and pure drug EHBR in 0.1N HCl

CONCLUSION

The optimized FDF FN2 had good mechanical strength, with uniform thickness, high folding endurance, shorter DT and faster dissolution when compared to conventional tablets. The preparation of FDF did not require the addition of any disintegrant separately, so this formulation seems to be an attractive alternative to conventional marketed formulations.

CONFLICT OF INTERESTS

Declare none

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