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Research Article

Solubility Enhancement of Apixaban and Formulation of its Fast-Disintegrating Tablets

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ABSTRACT

The aim of the work was to enhance the dissolution rate of apixaban by preparing its solid dispersions (SDs) using hydrophilic carrier PEG 4000 and use the solid dispersion of the drug in formulation of dispersible tablets for patient compliance. The SDs of apixaban with PEG 4000 were prepared at 1:1, 1:2 and 1:3 w/w ratios by physical mixing, melting and solvent evaporation techniques. The used hydrophilic carriers showed a more than two-fold increase in dissolution rate in their prepared solid dispersions by melting or solvent evaporation techniques at 1:3 w/w ratio. The pure drug apixaban shows a dissolution rate of nearly 39 % after 60 m, whereas the solid dispersions by melting or solvent evaporation showed 80 % of dissolution after 45 m using phosphate buffer pH 6.8 as dissolution media and detected at 281 nm (λmax i.e., absorbance maxima for the drug). The FTIR spectroscopic and DCS thermal studies showed the compatibility of apixaban and the absence of well-defined drug polymer interactions, though the shift in peaks was observed due to the formation of new bonds. It was found that crospovidone at 5 % concentration of the tablet weight showed the satisfactory result of dispersion in few seconds.

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Introduction

Oral administration widely utilized route, as have benefits of self-administration, there is no pain. (1, 2). Understanding of various disciplines, including GI physiology, PK-PD and formulation design is required for the development of dosage forms (3-4).

Dispersion and absorption within the oral cavity also permit intra-oral absorption, thus by passing first-pass effect (5). It is convenient and economical method of drug delivery having the highest patient compliance (6-8). The FDTs has been gaining demand for more friendly patient compliance dosage forms. Oral absorption overcomes the adverse effect to some extent (9-11). The FDTs which disintegrate rapidly in the oral cavity within 1 min. E.P 7.0, says FDTs should be disintegrated in less than 3 minutes. Dispersible tablets are uncoated tablets that are dissolved in water before being administered, resulting in a uniform dispersion. Bitter drugs are more acceptable to different groups of people when the tablets dispersed with a good taste and flavour. When put in water, the tablets must be able to form an adequate dispersion that is uniform and stable. The main advantage is that the absorption and onset of clinical effects are faster (12-15). One such approach of formulating a convenient dosage form is FDTs (16-18).

The objective of the present work is preparation of ODTs of apixaban whose solubility has been improved by preparing their solid dispersions, using super-disintegrants.

Apixaban is a category of an antithrombins and anticoagulants category of drug molecule. Belongs to BCS class II, used for reducing strokes and systemic embolisms, treatment of deep venous thrombosis (DVT) and pulmonary embolism (PE)

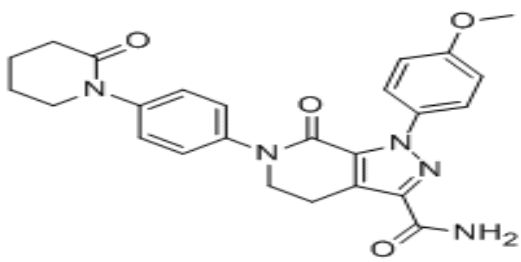

Figure 1: Structure of Apixaban

The prepared tablets are having acceptable mechanical properties and faster disintegration to achieve faster onset of action, improved bioavailability. The ODTs are aimed to overcome the difficulties like swallowing, vomiting and to bypass the first pass metabolism.

MATERIALS AND METHODS

Apixaban as gift sample was obtained from DRL, Hyderabad and the super-disintegrants sodium starch glycolate, croscarmellose sodium (Ac-di-sol) and crospovidone were obtained from Alembic Ltd, Ahmedabad, India. Aerosil, Mannitol,

Microcrystalline cellulose and all ingredients were of analytical grades.

PREPARATION OF FAST DISINTEGRATING TABLETS:

The FDTs of apixaban SD were prepared by direct compression method using three different super disintegrants and formulae given in Table No. 1. FDTs were prepared with a total weight of 200 mg of varying polymer compositions and fixed quantity of apixaban of 10 mg.

Table 1: Formulation of apixaban fast disintegrating tablets

Sl.No.	Content (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Apixaban SD (equivalent to 10 mg of drug)	30	30	30	30	30	30	30	30	30
2.	Crospovidone	6	12	18	-	-	-	-	-	-
3.	Sodium starch glycolate	-	-	-	6	12	18	-	-	-
4.	Croscarmellose sodium (Ac-Di-Sol)	-	-	-	-	-	-	6	12	18
5.	Pearlitol SD 200	50	50	50	50	50	50	50	50	50
6.	Microcrystalline cellulose	110	104	98	110	104	98	110	104	98
7.	Magnesium stearate	2	2	2	2	2	2	2	2	2
8.	Aerosil	2	2	2	2	2	2	2	2	2
	Total weight	200	200	200	200	200	200	200	2000	200

The specified quantity of API and superdisintegrants were weighed, mixed and passed through sieve #40. Mixed in geometrical order and blended up to 10mins, except magnesium stearate and aerosil. Prior to the compression the magnesium stearate and aerosil were added and mixed gently for 1-2 min. The tablets were punched using flat faced 8 mm punches. The hardness was adjusted to (2-3.5 kg/cm^2).

CHARACTERIZATION:

Drug-excipients compatibility studies:

The compatibility studies were done by IR spectra analysis

Post compression evaluation of formulations:

Evaluation of post-compression:

Post-compression parameters such as weight variation, thickness, hardness, friability, wetting time, water absorption ratio, *in vitro* dispersion time, disintegration test, content uniformity and

in vitro dissolution study were determined.

Wetting Time and Water Absorption Ratio:

The Wetting Time of the tablets was determined. This experiment was conducted to mimic the action of saliva in contact with tablet. A Whatman filter paper disk folded once diametrically was placed in a petri dish. A small volume (10 ml) of water containing the water-soluble dye was added to the filter paper on the petri dish. The tablet was carefully placed on the filter paper at t = 0 and the time for complete wetting were measured. Complete coloring the tablet was taken as a sign for complete wetting. The wetted tablet was then weighed and water AR was determined according to Equation mentioned below

Absorption Ratio = 100 X (Wa – Wb) /Wb

Where Wa and Wb are the tablet weights after and before wetting

In vitro dispersion time:

The dispersion time of the tablets was evaluated. Two tablets were placed in a beaker containing 100 mL of phosphate buffer pH 6.8 at 37±0.5 ºC. It is waited for three minutes after which the beaker content is poured on a sieve (22 mesh, i. e., 710 µm), no residue should remain over the sieve.

RESULTS AND DISCUSSION

Compatibility studies: The compatibility studies were performed using Fourier transform infrared spectroscopy

IR Spectra: IR spectra of apixaban, SSG, Ac-di-Sol, crospovidone, and drug superdisintegrant mixture at 1:1 ratio was prepared and checked the spectra. No interaction between the drug and the superdisintegrants was found as important peaks for apixaban was retained in the drug super-disintegrant-mixture.

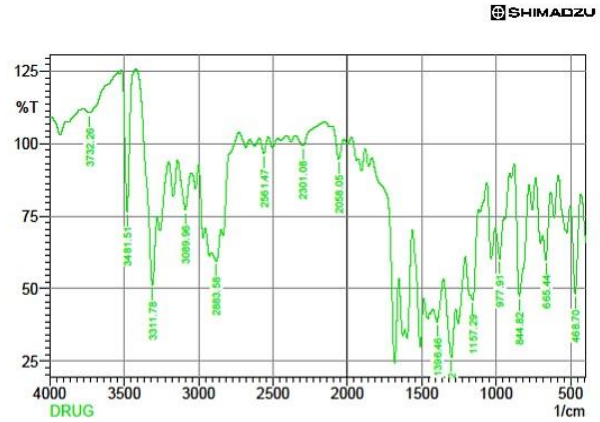

Figure 2: IR-Apixaban

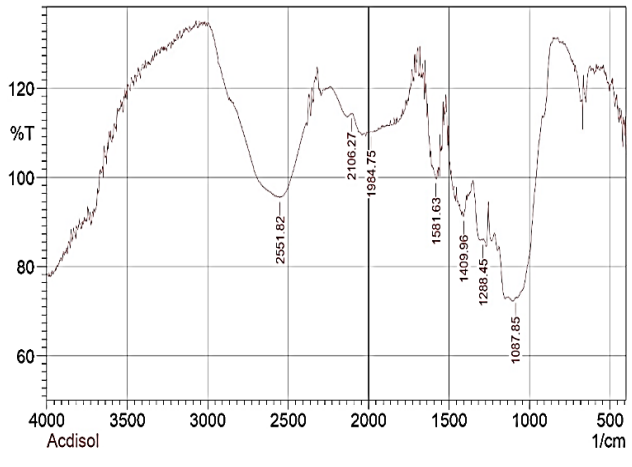

Figure 3: IR spectra-Ac-di-sol

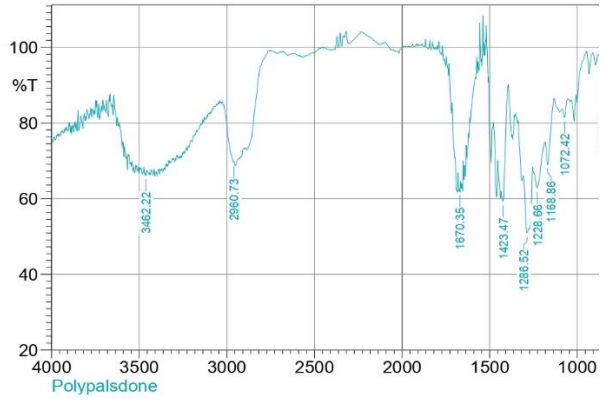

Figure 4: IR spectra-crospovidone

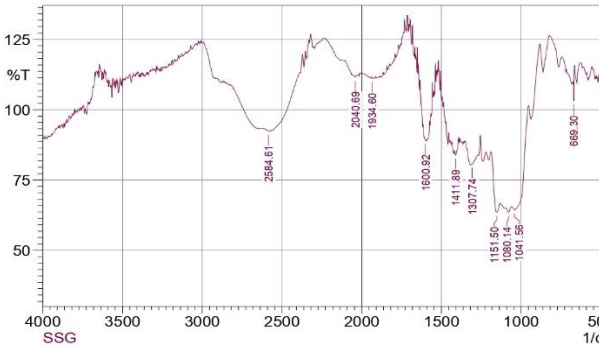

Figure 5: IR spectra-SSG

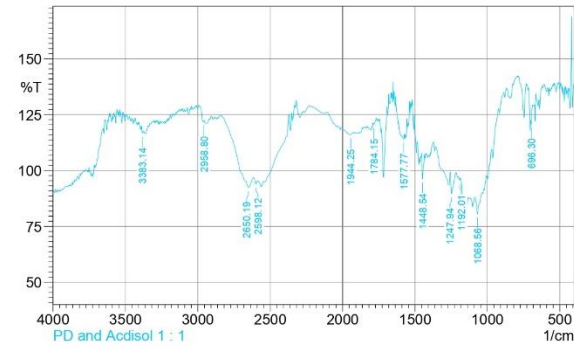

Figure 6: IR spectra-apixaban-Ac-di-sol (1:1)

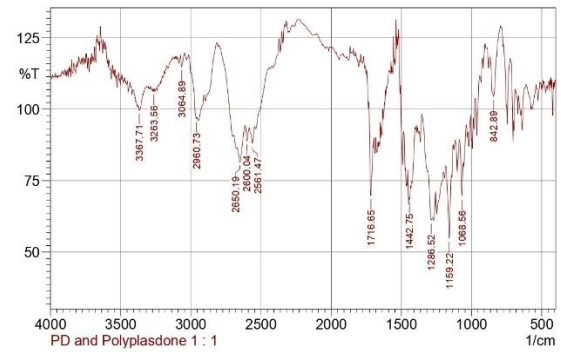

Figure 7: IR spectra-apixaban-crospovidone-1:1

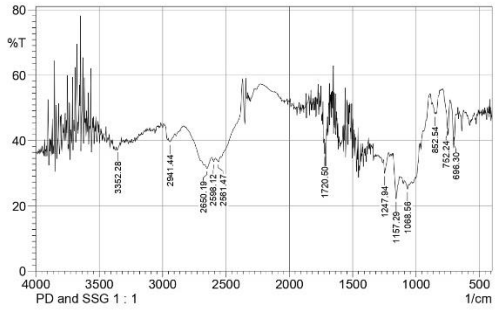

Figure 8: IR spectra-apixaban-SSG (1:1)

Pre-compression evaluation:

The theta was 25° - 30° shows, good flow. The bulk density and tapped density for the formulations were calculated. The value ranges from 0.251 to 0.257 g/cm^3 and 0.258 to 0.283 g/cm^3. The Carr's index of various formulations was calculated. The C.I and H.R of pre compressed blends was in the range of 11.80 % to 16.30 % and 1.09 to 1.20 respectively.

Post compression results

The results of F1 to F9 were given in Table 2.

Weight variation Test:

Weight variation results were found to be within specification ± 7.5 % as per I.P.

Thickness measurement:

The thickness of all the formulations was in the range of 3.21 to 3.23 mm.

Hardness test:

The hardness test results were in the range of 2.5 to 3.5 kg/cm².

Friability test:

Found to be <1.0% and was within the specification. The results were in the range

of 0.52 to 0.83 % and for optimized formulation the friability was found to be 0.59 %.

Disintegration test:

Disintegration results were found to be within the specification i.e., within 1 minute.

Wetting time test:

About 30-47 sec

Drug content study:

Found to be 100.5 %.

Table 2: Post compression parameters of prepared ODT tablets of apixaban.

F- Code	Wt. variation (kg/cm^2)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	D.T (sec)	Wetting time (sec)	Drug content (%)
F1	198.7±0.11	3±0.14	2.5±0.21	0.61	40.22±1.61	30.05±0.25	99.3±0.56
F2	201.5±0.12	3±0.16	2.7±0.11	0.59	26.53±1.24	37.14±0.14	100.5±0.51
F3	198.1±0.13	3±0.18	2.6±0.30	0.52	31.34±1.22	39.13±0.06	100.3±0.68
F4	197.5±0.11	3±0.24	3.0±0.50	0.45	29.22±1.44	42.41±0.72	99.4±0.21
F5	195.4±0.14	3±0.23	3.1±0.10	0.66	56.43±1.35	31.22±0.15	99.6±0.26
F6	198.3±0.12	3±0.15	3.1±0.30	0.71	51.36±1.32	32.35±0.72	100.2±0.67
F7	199.5±0.13	3±0.18	3.3±0.30	0.68	23.04±1.06	36.57±0.71	99.8±0.45
F8	197.2±0.11	3±0.22	3.1±0.24	0.70	22.41±1.03	47.40±0.67	101.1±0.35
F9	196.8±0.14	3±0.15	3.4±0.11	0.72	30.25±1.32	35.22±0.98	99.6±0.64

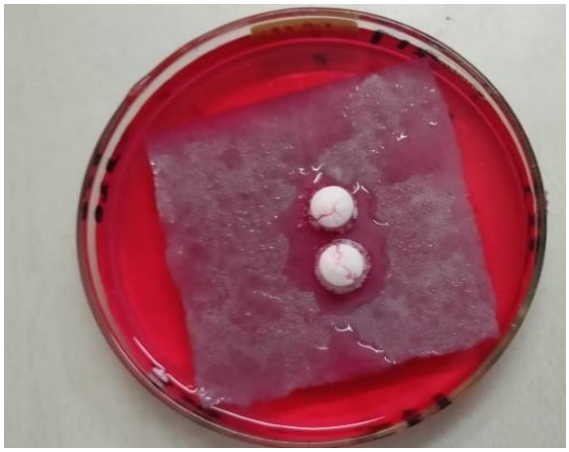

Figure 9: Wetting time and water absorption ratio

Drug release studies:

The drug release is shown in Fig 5. It was observed that the formulations were able to release more than 70 % of drug within 30 min and with crospovidone it showed more than 75 % after 30 m. Among the optimized formulations, F2 formulation (i.e., with crospovidone at 6%) is good because of its lowest disintegration time, dispersion time, wetting time and highest drug release.

Table 3: Dissolution profile optimized formulations of FDT

Time (m)	%Cumulative Drug Release		
	F2	F6	F9
0	0	0	0
5	45.8	42.6	44.7
10	50.2	45.3	47.4
20	59.6	57.3	58.4
30	75.6	73.9	74.3
45	82.5	81.25	81.15
60	96.38	94.84	95.13

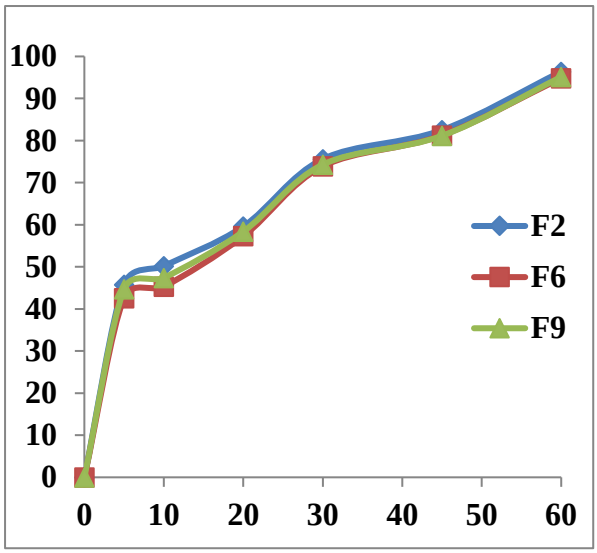

Figure 10: Dissolution profile optimized formulations of FDT

CONCLUSIONS:

Fast disintegrating tablets were prepared using super-disintegrating agents at 3%, 6 % and 9 % concentration of tablet weight. Among all the formulations (i.e., nine formulations) formulation containing 6 % of crospovidone showed satisfactory results. There is no incompatibility observed between the drug and the used super-disintegrating agents as the characteristic peaks for the drug were retained in the mixture in the IR spectra. Fast disintegrating tablets have wide scope for many drugs; mostly for their use by geriatrics and pediatrics while considering their convenience and therapeutic efficacy.

CONFLICT OF INTEREST: There is no conflict of interest for this work and publication.

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