Lampyrid 2023: Volume 13, 605–618
ISSN: 2041-4900
https://lampyridjournal.com

Formulation, Evaluation and Comparison Study of Sublingual Tablets of Flubendazole with Solid Dispersed Sublingual Tablets of Flubendazole for Prophylaxis of Filariasis

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Abstract
This investigation is concerned with formulation of oral dosage form for prophylaxis of filariasis with sublingual tablets.
A macrofilaricide such as Flubendazole would be extremely helpful in the effort to eradicate human filariases. The need for alternative pharmacological techniques to enhance the systemic bioavailability of Flubendazole and its metabolites has become more urgent as a result of significant injection site reactions being observed in humans after parenteral Flubendazole treatment. Oral mucosal delivery of drugs promotes rapid absorption and high bioavailability, with a subsequent immediate onset of pharmacological effect along with patient convenience and compliance.
The present study, aims to develop sublingual tablets of Flubendazole. Different concentrations of superdisintegrant Crospovidone were added. Mannitol was added in appropriate ratios for taste masking.
The study involved formulation of solid dispersion system of Flubendazole to enhance soubility and hence bioavailability. Drug content and in vitro studies were carried out on the formulation. All formulation of pure drug and solid dispersion system were compressed by direct compression method. These tablets were evaluated as final dosage form for drug content and in vitro release profile.
A comparative study of all dosage form was carried out. In vitro release studies were carried out mimicking in vivo conditions in the sublingual region for dissolution. It was seen that solid dispersion drug delivery system formulation SD3 showed maximum release of 93.56% after 18 minutes as compared to F3 formulation.
Thus it was concluded that solid dispersion delivery system of Flubendazole can be a better option for the prophylaxis of filariasis.

Keyowords: Prophylaxis Filariasis Sublingual Bioavailability

1. Introduction:

Lymphatic filariasis (LF), sometimes known as elephantiasis, affects over 128 million people, primarily in Africa and South-East Asia. it is caused by filarial nematodes of the superfamily Filarioidea, sometimes referred to as "filariae.".This can lead to temporary or permanent disability, decreased physical productivity, lost income, and social stigma[1]. One of the main causes of blindness in the world, onchocerciasis, often known as river blindness, affects over 26 million people in Africa, leaving 746,000 with visual impairment and 265,000 completely blind[1]
River blindness is caused by Onchocerca volvulus, while lymphatic filariasis is brought on by Wuchereria bancrofti, Brugia malayi, and Brugia timori.[1]
Blood-feeding insects spread filariae's infectious larvae, which develop into reproductive adults many months after infection. Host immune deficiency leads to persistent, chronic infections[1]
Despite the severity of the problem, there is optimism over the chances for the eradication of LF, and onchocerciasis[2]. Addressing the issues with the current chemotherapy will help to eliminate the crippling diseases onchocerciasis and filariasis (LF), which are a significant contributor to long-term disability and a barrier to socioeconomic progress (World Health Organisation, 1995, World Health Organisation, 2010)[3]

The three drugs utilised in the current control programmes are albendazole (ABZ), ivermectin (IVM), and diethylcarbamazine (DEC). All three are safe and available for donation. In the regimens used, DEC has a limited adulticidal efficacy and permanently renders immature stages of the host (microfilaria) sterile[1]. Due to the possibility of serious and intolerably unpleasant side effects on an infected person's eyes and skin as well as during pregnancy, it is not recommended in places where onchocerciasis is common. IVM is a microfilaricide that, in addition to killing adult worms for a long time, also sterilises the host for at least six months to prevent re-infection with microfilariae. IVM, however, needs to be given at least once a year. IVM, like DEC, has negligible macrofilaricidal effects on people or other animals, therefore it takes much longer to eradicate it through mass drug administration. Last but not least, in lymphatic filariasis control programmes, ABZ is generally given to annual DEC or IVM treatments. It's still up for debate whether combination therapy is better than DEC or IVM alone because it's unknown what the benzimidazole (ABZ) component of this regimen does in terms of activity. Therefore, the only strategies capable of effectively controlling human filarial infections at this time are those that primarily focus on eliminating macrofilariae and permanently stopping their development. It is now widely recognised that adding a macrofilaricidal chemical to current management strategies will increase the likelihood that attempts to control filariasis will be successful in a timely

manner. [1]

Flubendazole (FBZ) is a methylcarbamate benzimidazole (BZD) that is extremely effective against human gastrointestinal nematodes. It inhibits glucose uptake and microtubule formation. Additionally, historical data show that flubendazole subcutaneous injections have a macrofilaricidal effect that can eliminate up to 100% of adult filariae. For this reason, flubendazole is frequently used as a positive control in filariasis experimental animal studies examining direct-acting drugs. These historical data indicate that FBZ has remarkable effectiveness against filarial nematodes with repeated parenteral dosing.[4]

Like other BZDs, FLBZ has a low systemic bioavailability and is marketed for oral use in humans as tablets or solutions. The macrofilaricidal efficacy of FLBZ is thought to need continuous systemic exposure, which is not attained by consuming conventional oral formulations. It has been demonstrated that FLBZ has in vivo activity against a variety of filariid species after being delivered parenterally in both animal and human investigations. The Need for professional assistance for administration of drug, serious pain at the site of injection and lack of patient compliance has given rise to the need for an efficient and effective alternate route of administration to the parenteral administration of flubendazole.[1]

Several techniques are available to enhance the solubility and bioavailability of the Flubendazole such as solvent electrospinning, Solvent electrospun nanofibres, co amorphization, solid dispersion etc.[5,6.7.8]

The goal of the current study was to find the alternate delivery to parentral dosage of flubendazole to eliminate the side effects caused at the site of injection and also increase the solubility by solid dispersion method and hence sublingual tablets were formulated. sublingual tablet formulations help in rapid absorbtion and high bioavailability, with a subsequent immediate onset of pharmacological effect along with patient convenience and compliance.

2. Materials and methods:

Material

Flubendazole was purchased from Prince Scientific, Hyderabad, Telangana, India. Microcrystalline cellulose, Crospovidone, Magnesium stearate, Talc, Menthol, Mannitol, Sodium Saccharine, Urea were purchased from shop no. 11/15, Harsh plaza, Bhoi lane, Near chapekar chowk, Chinchwad, Pune. All other remaining materials used were of analytical grade

Method

i. Standardisation (calibration curve)

An accurately weighed quantity of Flubendazole (10mg) was transferred to 100 ml volumetric flask, dissolved in 10 ml of DMF solution and the final volume was made upto 100 ml with Ethanol to get a stock solution A. From this stock solution A, 2 to 10ml were pipetted out and made upto 10ml with Ethanol in 10ml volumetric

flask to get the solution in the range of 2-10μg/ml concentration and absorbance was recorded at 200-400 nm by UV visible spectrophotometer (UV 1700 Shimadzu) at λ max of drug and results were recorded. The calibration graph was plotted as concentration on x-axis and absorbance on y-axis.[9]

ii. Identification Of Drug Sample By FTIR

Pure drug's FTIR spectrum was analysed. The sample was examined using FTIR spectroscopy and the KBr pellet technique. Potassium bromide and Flubendazole were combined in an amount of around 10 mg. The spectra was examined throughout the 4000–400 cm–1 frequency band.[10]

iii. Drug Excipient compatibility study

Drug-excipient interaction study was used to evaluate the drug's compatibility with the excipient. combination of drug with excipients were subjected for IR spectroscopic study, to ascertain whether there is any interaction between the drug and excipients used[10]

iv. Formulation of sublingual tablets

Sublingual tablets of Flubendazole were prepared by direct compression. Mannitol was added to the drug in the ratio of 1:1 for taste masking. All ingredients were passed through a #80 mesh separately. Then the ingredients were weighed and mixed in geometrical order and compressed into tablets of 250 mg by direct compression method using 6-mm bi-concave punches on a Double Rotary Tablet Compression Machine (Rimek 10 station minipress). Batches F1-F8 prepared were taste-masked by making a physical mixture with mannitol. Batch SD3 was prepared by solid dispersion method using urea as a carrier with the optimized formulation from batches F1-F8. The compositions of batches F1-F8 and batch SD3 are shown in Table [11]

v. Preparation of solid dispersion:

It was attempted to improve the aqueous solubility of Flubendazole by solid dispersion. The solvent evaporation method and physical mixing were used to create solid dispersions of Flubendazole.[12]

a. Physical mixing method

50 mg of flubendazole was taken in a china dish to which equal amounts of urea as a carrier was added. Dimethylformamide solvent was then added to this blend and mixed thoroughly.[12]

b. Solvent evaporation method

Solvent evaporation method was used in this solid dispersion technique. The mixture was heated to a predetermined temperature while being constantly stirred to evaporate the solvent, resultant drug was then allowed to cool and then kept in a desiccator for 12 hours after which it was gathered, ground in a

mortar and pestle for five minutes, and then run through sieve no. 80 to be tested for precompression parameters[12]

VI Formulation of sublingual tablet of solid dispersion of Flubendazole

c. Flubendazole sublingual tablets by solid dispersion technique were created. The solid dispersion powder system was used to prepare the sublingual tablets by direct compression method and a comparison study was carried out. Table 1 displays general formulation information for sublingual tablets.

vi. Evaluation of Sublingual tablets:

a. **Weight Variation**: The weight variation was carried out by weighing 20 randomly selected sublingual tablets from each batch. The average weight was calculated and compared with the individual sublingual tablet weights.[13]

Table 1 :Percentage deviation in weight variation

Average weight of the tablet	% deviation
80mg or less	±10
More than 80 mg but less than 250 mg	±7.5
250 mg or more	±5

b. **Thickness**: Ten tablets were randomly selected from each batch and the thickness of each individual tablet was measured using a Digital Vernier Calliper.[14]

c. **Disintegration time**: The disintegration time for sublingual tablets was evaluated using the usual test for tablets as stated in the pharmacopoeia. Tablets were inserted in the disintegration tubes and the time necessary for full breakdown, that is without leaving any residues on the screen was recorded as disintegration time.[15]

d. **Hardness**: 10 tablets were randomly selected from each formulation and the hardness of each tablet was determined using Pfizer hardness tester. It was expressed in kg/cm^2 [14]

e. **Friability**: The roche friabilator test apparatus was used to weigh and place 20 tablets. The tablets were then subjected to rolling and repeated shocks from free falls within the test apparatus. The tablets were again weighed and de-dusted after 100 iterations. The percentage weight loss of the tablets was used to calculate their friability.[15]

f. **Drug Content**: The sublingual tablets were powdered. Powder equivalent to the dose of one tablet was weighed accurately. Powder equivalent to the dose of flubendazole was weighed and transferred to a 100 ml volumetric flask and volume was made up using methanol. Further, 1 ml of this solution was withdrawn and transferred to a 10 ml flask and volume was made up using methanol. Further dilutions were done suitably and UV absorbance was taken at 282 nm. [14]

g. **In - vitro Release Study**: The in-vitro drug release studies were carried out in dissolution apparatus USP type I. sublingual tablets containing equivalent dose of either of the drugs was added into 00 size capsules and placed in the basket of the dissolution apparatus containing phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5°. 5 ml samples were withdrawn at intervals of 2 min. Samples were analyzed spectrophotometrically at 282 nm with suitable dilutions and the percentage drug release was calculated. Graphs of percentage drug release versus time were plotted[14]

vii. **Evaluation of solid dispersion of Flubendazole**

% Drug content of solid dispersion

Solid dispersion equivalent to 10 mg of Flubendazole was weighed and dissolved in 10 ml of DMF. The solutions were filtered through filter paper and diluted suitably. The drug content in solid dispersion was calculated by using UV-Visible spectrophotometer (UV-1800, Shimadzu, Japan) at 282 nm.

Results and Discussion

Calibration Curve

Fig 1 shows standard calibration curve in DMF. The absorption reading with standard solution containing 2-10μg/ml of the drug was observed with slope of 0.07, intercept of 0.013 and regression coefficient value of 0.999.

Table 2: shows concentration and absorbance of Flubendazole at 282 nm

Sr No.	Concentration ($\mu g/ml$)	Absorbance at 282nm
1	2	0.00125
2	4	0.014
3	6	0.0288
4	8	0.0424
5	10	0.057

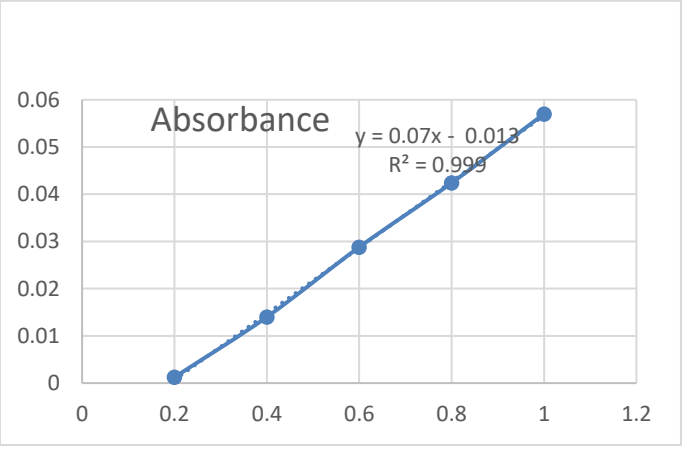

Figure no 1: Calibration curve of Flubendazole in DMF

The FT-IR and DSC study did not show any possibility of interaction between Flubendazole and excipients (Fig 2,3,4 5,6 and 7)

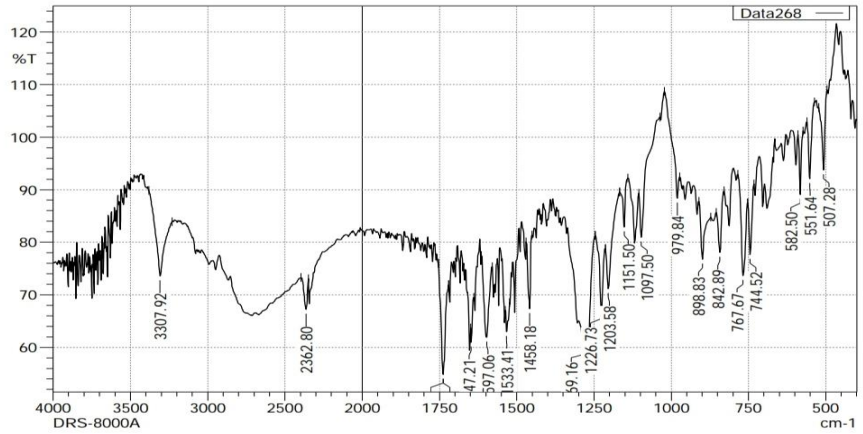

Figure 2 FTIR spectrum of Flubendazole

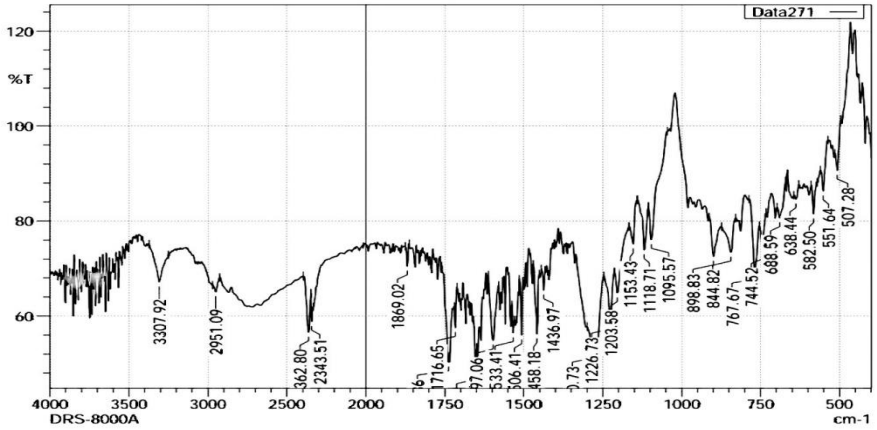

Figure 3 FTIR spectrum of drug+ crospovidone

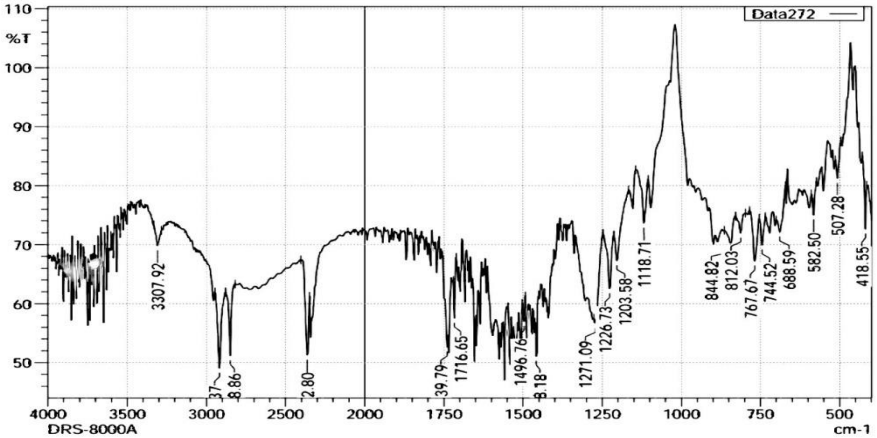

Figure 4 FTIR spectrum of drug+magnesium stearate

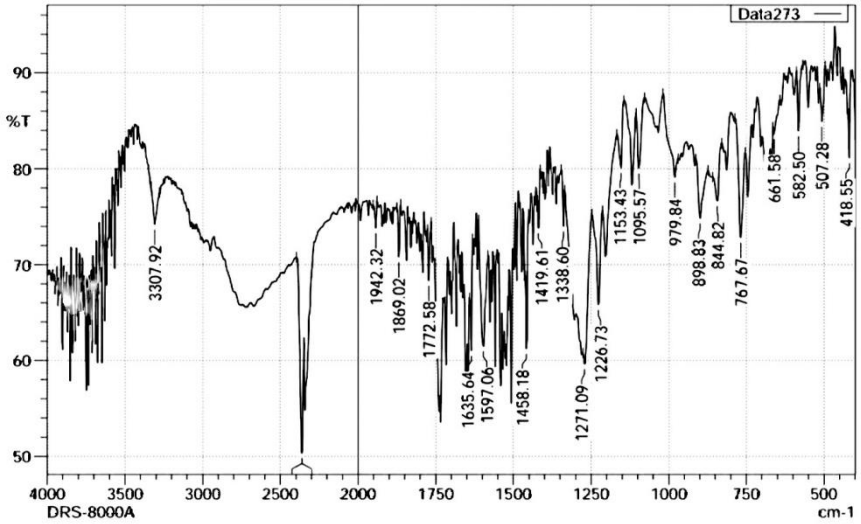

Figure 5 FTIR spectrum of drug+talc

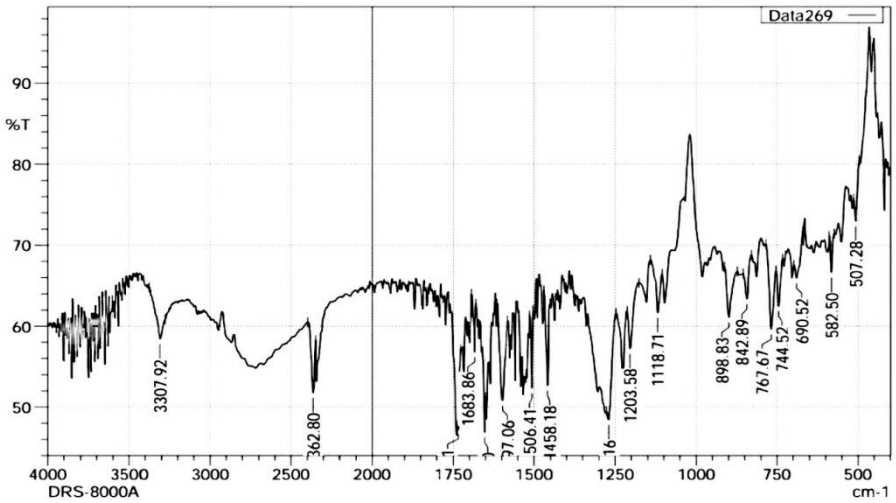

Figure 6 FTIR spectrum of drug+MCC

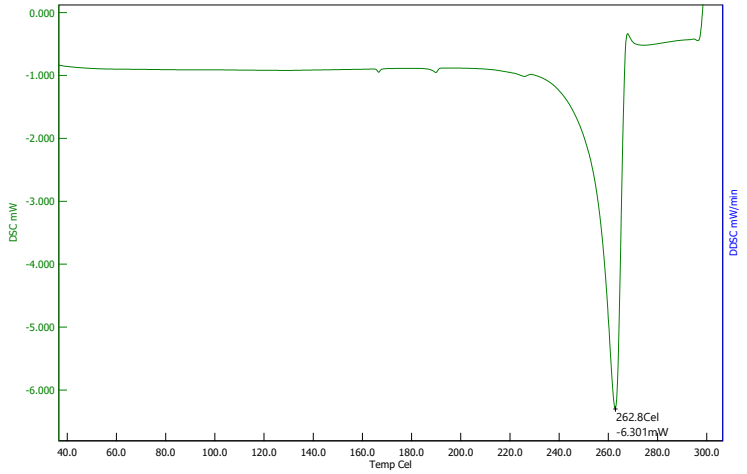

Figure 7 DSC study of Flubendazole

Table no 3 :Formulation of batch F1-F9 by direct compression method

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Quantity in mg								
Drug + Mannitol	200	200	200	200	200	200	200	200
MCC	33.864	32	27.5	21.136	32	27.5	23	27.5
Cross PVP	10	12	10	10	8	12.82	8	7.17
Menthol	2	1	4	5	4	4	5	2
Sodium Saccharine	3	3	3	5	3	4	5	5
Mg Stearate	1	1	3	6	2	1	5	4
Talc	1	1	3	3	1	1.50	4	5
Total weight	250	250	250	250	250	250	250	250

Table no 4: Hardness, uniformity of weight, % friability, drug content and in vitro disintegration time of batches F1-F8

Formulation code	Hardness ($g/cm^{2)}$	Uniformity of weight (mg)	Friability (%)	Drug content (%)	In-vitro disintegration time (sec)
F1	3.29±0.06	250.55±0.006	0.45±0.10	92.1 ±0.54	124±0.57
F2	3.05±0.04	248.25±0.006	0.44 0.11	93.8 ±0.61	114±0.10
F3	3.51±0.06	249.3±0.006	0.55±0.18	96.6 ±0.34	106±1.5
F4	3.18±0.03	248.60±0.005	0.55±0.14	93.32 ±0.70	109±0.58
F5	3.62±0.07	248.75±0.006	0.43± 0.11	90.91 ±0.54	122±0.57
F6	3.42±0.04	251.95±0.003	0.38±0.09	94 ±0.40	112±0.55
F7	3.73±0.03	248.25±0.004	0.37±0.05	90.4±0.75	113±0.57
F8	3.21±0.05	247.00±o.003	0.40±0.12	87.41±0.77	118±0.12

Percentage drug content of all the formulations was found to be 87.41 to 96.6 of flubendazole which was within the acceptable limit.

It was noticed that Batch F3 released the drug more quickly than any other batch, (figure 4). In 18 minutes, Batch F3 demonstrated a total drug release of 76.82% with disintegration time of 106 seconds along with other acceptable post compression parameters and was therefore regarded as the optimal batch.

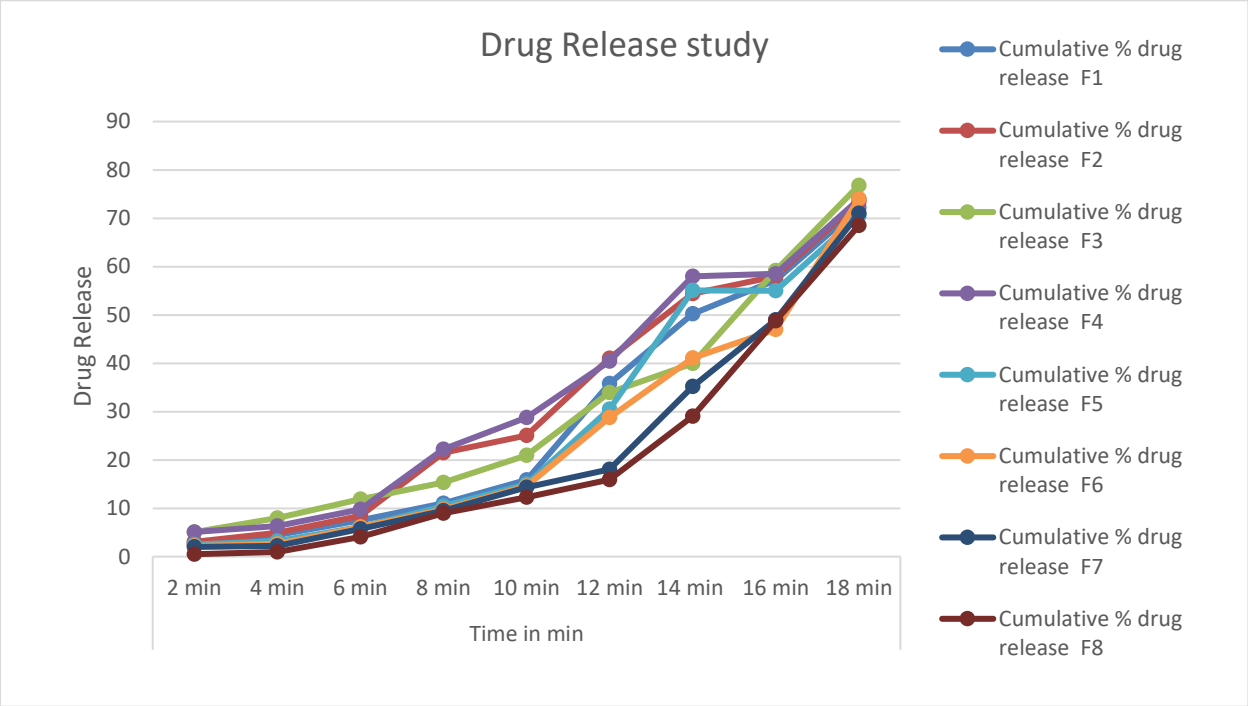

Figure 8: cumulative drug release upto 18 mins

Table 5: % cumulative drug release upto 18 mins

		Time in min								
		2 min	4 min	6 min	8 min	10 min	12 min	14 min	16 min	18 min
Cumulative % drug release	F1	2.9	4.5	7.5	11	15.87	35.8	50.21	57.2	72.2
	F2	3.06	4.95	8.47	21.5	25.1	41	54.4	58	73.4
	F3	5.07	8	11.9	15.35	20.93	33.91	40	59.19	76.8
	F4	5.1	6.3	9.8	22.2	28.8	40.43	58	58.5	73.92
	F5	2.5	3.2	6.1	10.4	15	30.5	55.1	55	70.5
	F6	2.2	2.6	6.16	9.8	14.6	28.8	41.08	47	74
	F7	2	2.2	5.7	9.5	14.31	18.06	35.2	49	71
	F8	0.5	0.97	4.10	9	12.3	15.9	29.02	48.8	68.5

The optimized batch F3 which showed the best characteristics after evaluation was selected for the formulation of the solid dispersion system. Cross povidone was used as the superdisintegrant, microcrystalline cellulose, mg stearate, talc were used in appropriate proportions. Since the dosage form must be held beneath the tongue, the formulation of the tablet included sweetening agents such mannitol and saccharine to make the dosage form more palatable. Table 3 displays general formulation information for sublingual tablets.

It was observed that development of sublingual tablets of batch 3 after solid dispersion of Flubendazole resulted in increased drug release after 18 mins as seen in fig 9.

After solid dispersion (SD3) batch showed 93.56% drug release within 18 minutes.

Table 6: % drug release of (pure drug) sublingual tablets and post solid dispersion (SD3) sublingual tablets of Flubendazole

Time	% drug release (pure drug)	% drug release (SD 3 batch)
2	0.45	10.09
4	5.54	35.57
6	8.25	55.17
8	30.78	55.88
10	52.17	58.73
12	55.43	59.68
14	60	64.82
16	70.47	78.57
18	76.82	93.56

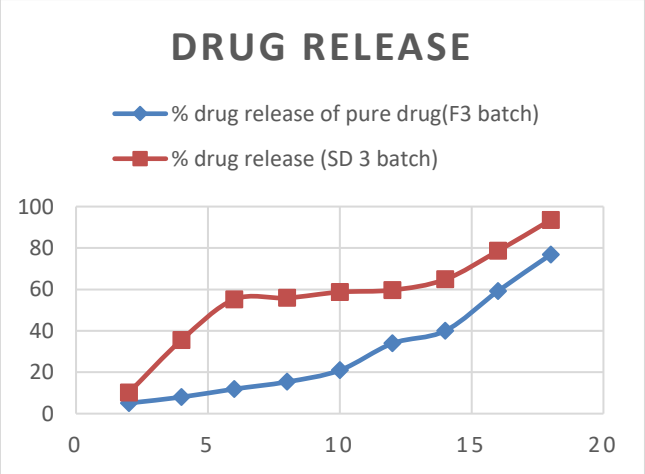

Figure 9 Comparison of % drug release of (pure drug) sublingual tablets and post solid dispersion sublingual tablets of Flubendazole

Stability studies

Table 7 displays the findings of the stability study. The stability experiments on the SD3 Formulation were conducted in the stability chamber for a period a month. The tablets were kept in a freezer at 40°C±2°C, and 75±5% relative humidity, Q1C as per the ICH guidelines. The tablets were periodically taken out with a 30-day interval and examined for parameters such as weight uniformity, hardness and percent drug content. The study's overall findings revealed that the formulation was stable.

Table 7: Stability study for sublingual tablet of SD3 Formulation

Parameter	0 days	15 days	30 days	Result
Weight uniformity (mg)	**249.3±0.03**	**249.3±0.03**	**249.3±0.03**	**No change**
Hardness (kg/cm^2)	**3.51±0.06**	**3.51±0.06**	**3.51±0.06**	**No change**
% drug content	**82.56±0.34**	**82.54±0.34**	**82.50±0.30**	**some change**

Conclusion:

The present study was carried out to develop sublingual tablets of Flubendazole and further enhance their bioavailability by Solid dispersion technique. Faster disintegration was achieved by the use of suitable superdisintegrant out of which the formulation F3 having 10 mg crospovidone and 27.5 mg MCC exhibited better results as compared to other formulations and was selected as the optimized batch. All the sublingual tablets were evaluated for parameters such as thickness, uniformity of weight, uniformity of content & in vitro drug release. Flubendazole solid dispersion formulation was prepared and evaluated for enhanced dissolution rate & bioavailability. The optimized formulation of pure drug (F3) showed 76.82 % percentage drug release which increased to 93.56% after solid dispersion. This shows that performing solid dispersion of poorly water soluble drug flubendazole enhances its dissolution rate and bioavailability. From the results of the research, it was concluded that the proposed aim of sublingual tablets of Flubendazole and its further solubility enhancement by solid dispersion technique for the prophylaxis of Filariasis was achieved successfully confirming the fulfillment of objectives of solubility enhancement as well as aiding patient convenience and compliance.

Conflict of Interest:

The authors have no conflict of interest regarding this investigation.

Acknowledgement:
I acknowledge and thank Dr. D.Y. College of Pharmacy, Akurdi for providing the necessary facilities to carry out my research work. I express my sincere thanks to Mrs. P.M. Choudhari, Principal Dr. N.S. Vyawahare , Mrs SP Mahaparale, Mr. M Mohite Assistant professor, Dr DY Patil College of Pharmacy, Akurdi for his support and guidance at every stage during the project work.

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