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Formulation and evalution of mouth dissolving tablet of solid dispersion by sublimation technique

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Abstract

Mouth dissolving tablets have recently taken an important market position by resolving issues with previous administration and leading to enhancing the patient's life, which have difficulty swallowing tablets. These tablets dissolve/disintegrate into the mouth for easy administration of pharmaceutical ingredients after introduction into the mouth without additional water. Some patients may find it inconvenient to have glass of water. A paediatric patient with allergies may use a dosage is better convenient than antihistamines. These tablets are also more convenient to some patients, who try to hide their daily dose under the tongue, especially schizophrenic patients. When preparing oral drug delivery system, simplicity of administration and improved patient compliances are must involve. The article aims to address ideal properties, advantages, limitations, selection of superdisintegrants and patented techniques of mouth dissolving tablet preparation.

Keywords: mouth dissolving tablets (MDTS), solid dispersion, direct compression, superdisintegrants, sublimation techniques, evaluation parameters,

Introduction

Many patients are difficulty in swallowing tablets, capsules and fluids especially elder patients. After many drug delivery innovations, the reason of self-medication, the oral route is the best suggested route for therapeutic administration and by observing the low-cost, accurate dosage and easy administration will give high patient compliances in this formulation. Tablets and capsules are the most commonly used dosage forms. but dysphagia is an important drawback to the conditions like mentally disabled persons, unconsciousness, motion sickness, elderly patients, parkinsonism and unavailability of water.

This technology involves the fast disintegration and quick dispersion, and also melt dissolve easily. The Food and Drug Administration (FDA) describes the MDTs formulation as 'a solid dosage form containing medicinal substances which disintegrate rapidly, normally within a matter of seconds, when introduces on the tongue.' These tablets are having very less disintegration time ranges from 15s to over a minute [1-3].

Significance of MDTs [4]

1. High rate of action & more accuracy of dosage.
2. MDTs gives better patient compliances.
3. High bioavailability as compared to the other formulation.
4. Cost effective & Easy administration of tablets.
5. Palatability is enhanced.
6. Packaging is easy and simple.

Limitations of MDTs [5]

1. Mechanical strength of the final product.
2. Stability is formed by drug and dosage.
3. Dissolution rate of the formulation of drugs in saliva.
4. Swallowability and mouth feel.
5. The rate of absorption in saliva solution.
6. Bioavailability overall.
7. Dryness of the mouth may not be good candidates for these tablet formulations due to reduced saliva production.

Materials and Methods

Materials

Sertraline HCl (Yarrow chem products, Mumbai), camphor (Yarrow chem products, Mumbai), HPβCD, sodium phosphate dibasic, sodium phosphate monobasic, sucralose, croscarmellose sodium, talc, magnesium stearate, mannitol, ethanol.

Preparation of drug-carrier complex by using solid dispersion method [7]

Drug and carrier (hydroxy propyl beta cyclodextrin) were prepared in the ratio of 1:3 by solvent evaporation method. The prepared drug-carrier complex material is used to punch or prepare sertraline HCl tablets by direct compression method.

Preparation of sertraline HCl mouth dissolving tablets [8]

The drug-carrier complex, diluents superdisintegrants, camphor and sucralose were passed through sieve no # 40. Talc and magnesium stearate are passed through sieve no # 80. All the above ingredients were properly mixed together and co-grinded in a glass pestle and motor. Then the mixed blend with excipients was compressed into a tablet on tablet

punching machine using 8 mm concave punch set. The compressed tablets are subjected to the process of sublimation in Hot air oven at 60^0C for 6h.

Spectroscopic studies [9]

Determination of λ-max

The stock solution of Sertraline HCl containing the concentration 18µg/ml was prepared in Phosphate buffer pH 6.8 and UV spectrum was taken using Shimadzu (UV-1201). The solution was scanned in the range of 200-400 nm.

Standard calibration curve of sertraline HCl

Preparation of standard stock solution A (1000 µg/ml)

Preparation of standard stock solution B (50 µg/ml)

5ml of above solution will be pipetted into 100ml volumetric flask and volume will be made with phosphate buffer pH 6.8 to give concentration of 50 µg/ml. Into a series of 10 ml volumetric flasks, aliquots of second standard solution 1ml, 2ml, 3ml, 4ml, 5ml and 6ml was added and the volume made up to 10 ml using pH 6.8 phosphate buffer. The absorbance of these solutions was measured against reagent blank at 275 nm using Shimadzu (UV-1201) UV spectrophotometer. Standard curve was plotted with concentration on x-axis and absorbance on y-axis.

Drug excipient compatibility study

The FTIR spectra of the drug with polymers were compared with the standard FTIR spectrum of the pure drug. For determining the compatibility of the drug with polymers, IR spectra of pure sertraline HCl and other ingredients like pure HPβCD, camphor, croscarmellose sodium, sucralose, talk, magnesium stearate, mannitol, physical mixture of drug and polymers were taken.

Characterization of Blends [10]

1. Bulk density (Db)

It is the ratio of total powder mass to bulk powder volume. It has been determined by pouring the heavy powder into the measuring cylinder (passed through std sieve #20) and the initial weight was noted. From this the bulk density is calculated according to the formula mentioned below.

$$Db = M/Vb$$

Tapped density (Dt)

The volume was measured with 750 tapping the powder and the tapped volume was found where there was less than a 2 per cent difference between these two volumes. If it is over 2%, tapping for 1250 times is continued, and the tapped amount has been recorded.

It is expressed in g/ml and is given by

$$Dt = M/Vt$$

2. Angle of repose (Θ)

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was also measured.

$$\Theta = \tan^{-1}(h/r)$$

3. Compressibility index

Carr's Index

The carr's index (C) is used to predict the compressibility and ease of flow of granulate and calculated as follows:

C = (Dt-Db)/ Dt*100, where Dt is tapped density and Db is bulk density.

Hausner's ratio

The hausner's ratio of the powder was determined by the following equation.

Hausner's ratio = Dt/ Db

Lower hausner's ratio (<1.25) indicates better flow properties than higher ones (>1.25).

Characterization of fast dissolving tablets [11-16]

Hardness test

Hardness (diametric crushing strength) is a force required to break a tablet across the diameter. The hardness was tested using Monsanto tester. "Hardness factor", the average of the three determinations, was determined and reported. The force was measured in kilograms per centimetre square (Kg/cm^2).

Friability Test

Friability is the loss of weight of tablet in the container/package, due to removal of fine particles from the surface. Permitted friability limit is 1.0 %. Roche Friabilator (Electro lab, Mumbai). Ten tablets were weighed collectively and placed in the chamber of the friabilator. In the friabilator, the tablets were exposed to rolling, resulting free fall of tablets (6 inches) within the chamber of the friabilator. It was rotated at a rate of 25 rpm. After 100 rotations (4 minutes), the tablets were taken out from the friabilator and intact tablets were again weighed collectively.

F=Initial weight x Final weight /Initial Weight x 100

Weight Uniformity Test

Fifteen tablets were weighed individually. The individual weights were compared with the average weight. The percentage difference in the weight variation should be within the permissible limits (±7.5%). The total weight of tablets formulated was 200 mg.

Drug content uniformity

Four tablets were weighed and crushed in a mortar. Then weighed powder contain equivalent to 100mg of drug transferred in 100ml of phosphate buffer. Its concentration 1000 mcg/ml. 10ml from this stock solution taken and diluted to 100ml of phosphate buffer, it makes 100mg/ml. Then 1.8ml from stock solution and diluted to 10ml. Absorbance measure at 275nm.

Thickness

Thickness of tablets indicates the strength to withstand compression force applied during manufacturing process. Thickness of tablets was measured by digital caliper.

In-vitro dispersion Time

In vitro dispersion time was measured by dropping a tablet into a Petri dish containing 10 ml of phosphate buffer pH 6.8 solution (simulated saliva fluid). Three tablets from each formulation were randomly selected and tested. *In vitro* dispersion time was found and expressed in seconds.

Wetting time

Two circular tissue papers of 10 cm diameter are placed in a Petri dish having the same inner diameter. 10ml of phosphate buffer solution, 6.8 pH containing Eosin, a water-soluble dye, is added to Petri dish. A tablet is carefully placed on the surface of the tissue paper so that complete tablet was not immersed in the solution. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time.

In vitro disintegration time:

The in-vitro disintegration time of a tablet was determined using disintegration test apparatus as per I.P. specifications. Six tablets were placed in the tubes of the basket and the time taken for the tablets to disintegrate was recorded as disintegration time (DT).

In vitro drug release

In vitro drug release of the samples was carried out using USP–type II dissolution apparatus (paddle type). The dissolution medium, 900 ml of phosphate buffer (pH 6.8) solution, was placed into the dissolution flask maintaining the temperature of 37±0.5 ºC and rpm of 50. One tablet was placed in each flask of dissolution apparatus. The apparatus was allowed to run for 10 min. Samples measuring 5 ml were withdrawn after every 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10min. Samples were filtered through 10 µm filter. The fresh dissolution medium was replaced every time to maintain sink condition. The collected samples were analyzed at 275nm using dissolution medium as blank. The cumulative percentage drug release was calculated.

Stability study [17]

The stability study of formulations was carried out according to the ICH guidelines. The optimum formulation (F2) was carried out by storing the tablets at 40 ± 2°C/75 ± 5% RH for 90 days in amber colored container in a stability chamber. At the end of 90 days tablets were tested for physical appearance, hardness, drug content disintegration and *In-vitro* drug release.

Result and Discussion

The aim of present study was to developing a dosage form with high porosity and enhanced bioavailability. The decrease in mean weight of tablets after sublimation corresponds to weight of camphor added as shown in Table 1. This study revealed that almost all of camphor had sublimated from the tablets. From the FTIR studies, the drug-polymers compatibilities were confirmed. *In-vitro* drug release studies the hardness of the tablet was in the range of 2.5-3.0kg/cm^2. Percentage friability of the tablet was less than 1. *in-vitro* dispersion time for tablets was in between 26- 47sec. Weight variation test results showed that the tablet was deviating from the average weight within the permissible limits of ±7.5%. finally, *in-vitro* drug release studies were carried out for a period of 8min, results showed that more than 90% of the drug was released from all the batches and the batch F2 consisting minimum concentrations of Camphor (5mg) and maximum concentrations of Croscarmellose sodium (5mg) shows a maximum released i.e., 99.68% of the drug within 5min.

Table 1: Formulation Design for the preparation of MDTs

Ingredients	F1	F2	F3	F4	F5	F6
drug-carrier complex (eq. to 25mg of drug) (mg)	100	100	100	100	100	100
Croscarmellose sodium	4	5	4	5	4	5
Camphor	5	5	10	10	15	15
Sucralose	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1
Talc	1	1	1	1	1	1
Mannitol	62	61	57	58	52	51
Total weight	175	175	175	175	175	175

Table 2: Precompression parameters of Sertraline hydrochloride tablet.

Formulation code	F1	F2	F3	F4	F5	F6
Angle of repose(Ɵ)	23.82	23.24	25.66	25.01	24.35	26.10
Bulk density(g/cc)	0.53	0.51	0.56	0.52	0.55	0.54
Tapped density(g/cc)	0.64	0.67	0.69	0.65	0.68	0.66
Carr's index (Carr, Jr)	13.72	15.26	19.35	14.61	18.51	14.63
Hausner's ratio	1.14	1.27	1.12	1.23	1.15	1.24

Table 3: Post-compression parameters of Sertraline HCl tablet.

Formulation code	Hardness (Kg/cm^2)	Friability (%)	Thickness (mm)	*In-vitro* disintegration time (sec)	Wetting time (sec)	*In-vitro* dispersion time (sec)	Weight Variation (%)	Drug content (%)
F1	2.56±0.12	0.54	2.59±0.03	27±1.6	25±2.3	29±2.4	0.55	99.32
F2	2.52±0.28	0.54	2.56±0.02	24±1.8	23±1.8	26±1.5	0.81	98.52
F3	2.71±0.12	0.57	2.67±0.10	31±1.4	29±1.2	35±3.4	0.78	99.06
F4	2.64±0.24	0.62	2.74±0.15	35±2.1	33±3.2	38±1.7	0.72	99.19
F5	2.9±0.36	0.64	2.65±0.01	39±2.8	37±2.2	44±2.5	0.86	97.72
F6	2.84±0.32	0.59	2.68±0.05	43±2.4	39±0.8	47±3.2	0.86	98.25

Table 4: Tablet weight (mg) before and after sublimation of camphor

Formulation code	Camphor (mg)	Sublimation (mg)	
		Before	After
F1	5	175.5	171.4
F2	5	175.2	171.4
F3	10	175.0	166.5
F4	10	175.1	166.6
F5	15	175.2	161.0
F6	15	175.2	161.2

Table 5: Data for calibration curve of Sertraline HCl at 275nm

Sl. No	Concentrations	Absorbance
1	0	0.00
2	5	0.19
3	10	0.38
4	15	0.57
5	20	0.75
6	25	0.93
7	30	1.11

Table 6: *In-vitro* Drug-release Profile of Sertraline HCl

Time	% drug release					
	F1	F2	F3	F4	F5	F6
00	0	0	0	0	0	0
01	14.75	21.85	14.30	14.28	18.27	8.98
02	28.02	54.11	38.39	35.89	35.35	21.88
03	51.14	79.58	58.76	56.16	56.00	47.78
04	79.95	94.43	77.14	77.21	72.30	60.98
05	96.90	99.68	90.49	96.36	91.66	82.46
06	98.99	99.68	97.26	99.14	95.94	90.42
07	98.99	99.68	99.16	99.30	98.84	95.75
08	98.99	99.68	99.16	99.30	99.57	99.13

Table 7: Stability data of the Sertraline HCl MDTs formulation F2

Formulation Code	Physical appearance	Hardness (Kg/cm^2)	In-vitro disintegration time (sec)	In-vitro dispersion time (sec)	Drug content (%)
At 25±2°C/ 60±5% RH	No Change	2.46 ± 0.11	26 ± 1.2	28 ± 1.6	97.16
At 40±2°C/ 70±5% RH	No Change	2.45 ± 0.15	26 ± 1.5	29 ± 1.1	97.10

Table 8: Stability data of % drug release study

Time (min)	% drug release	
	A	B
1	22.53	21.37
2	53.86	51.73
3	79.34	80.11
4	93.11	94.65
5	99.06	99.22
6	99.56	99.68

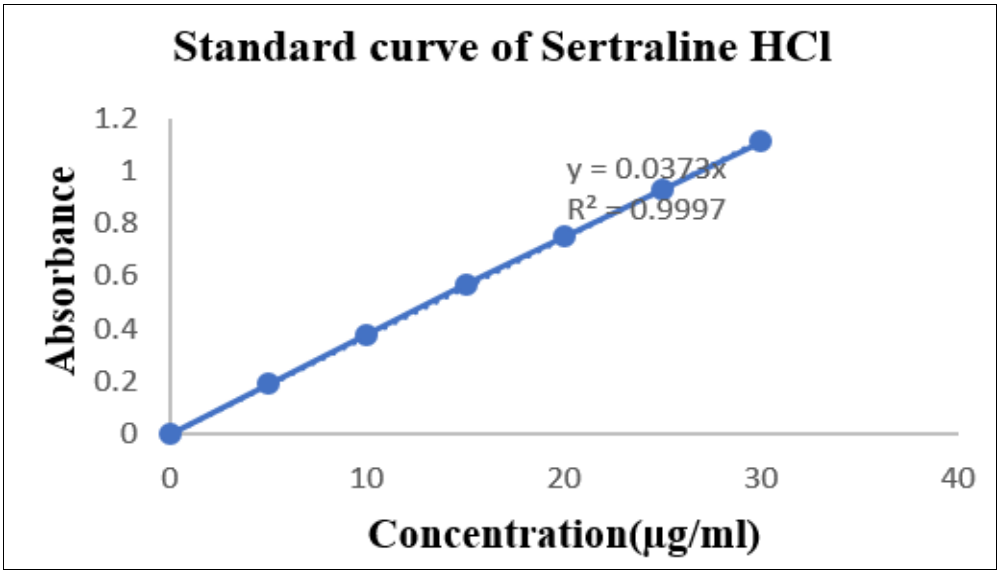

Fig 1: Standard calibration curve of Sertraline HCl

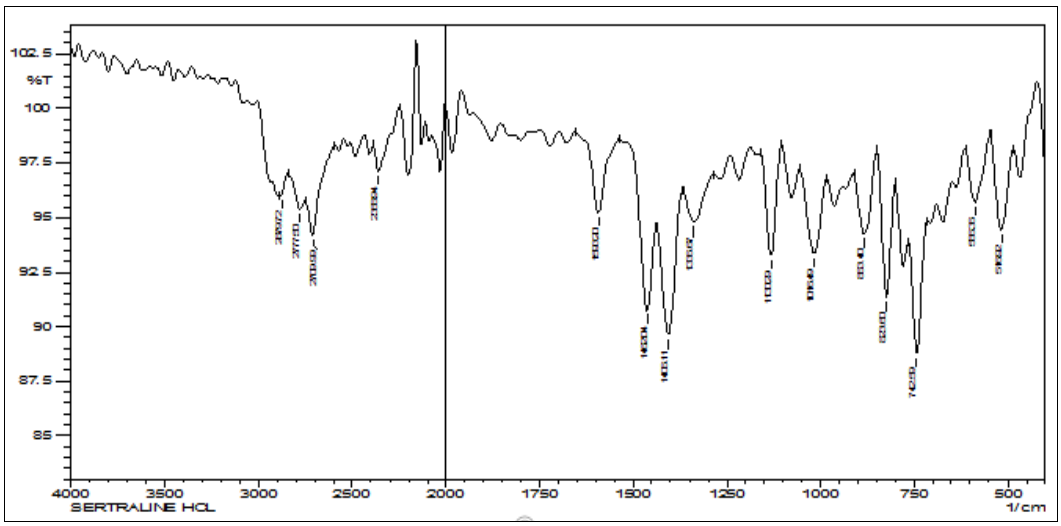

Fig 2: FTIR Spectra of Sertraline HCl

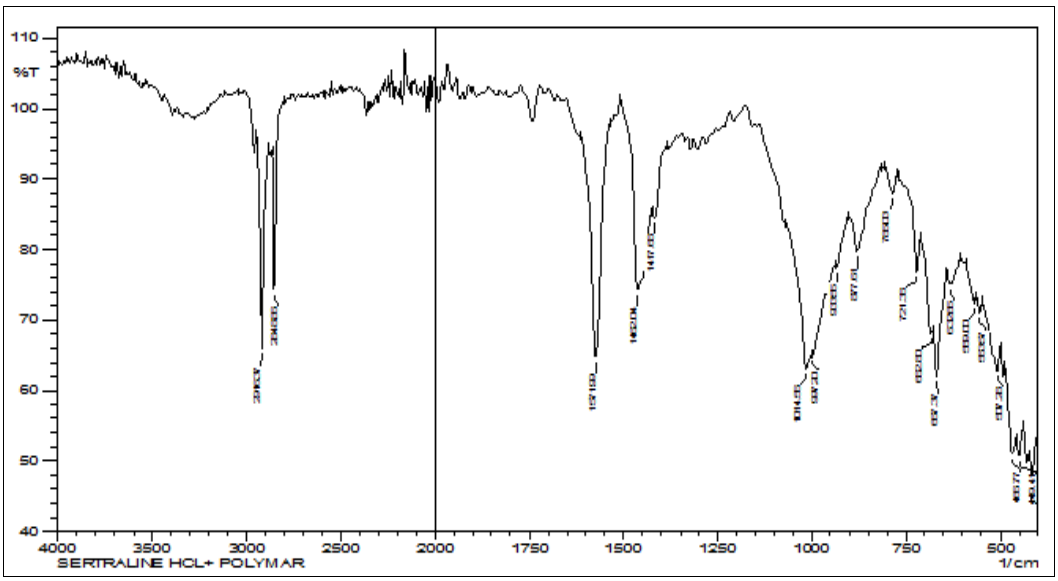

Fig 3: Sertraline HCl + HPβCD Complex

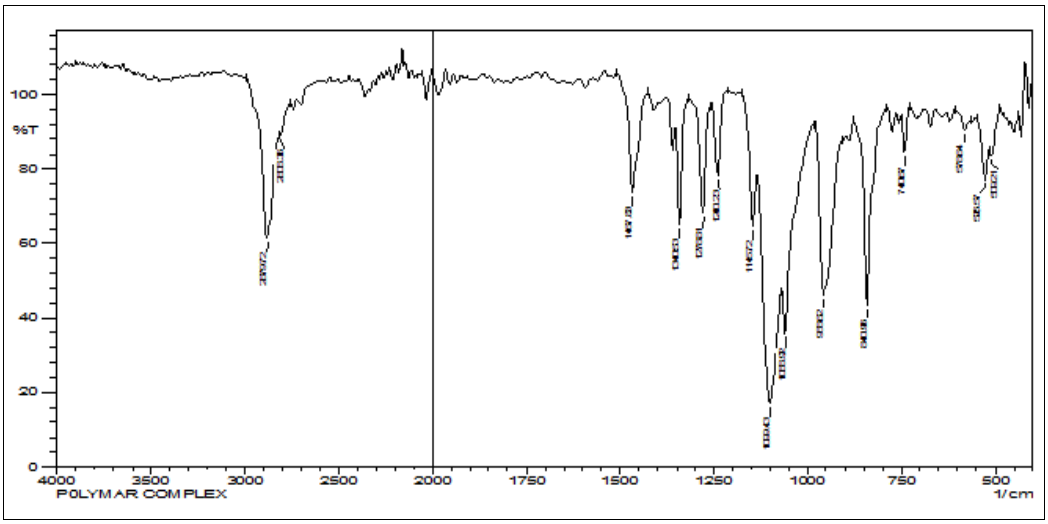

Fig 4: Sertraline HCl + HPβCD + Excipients

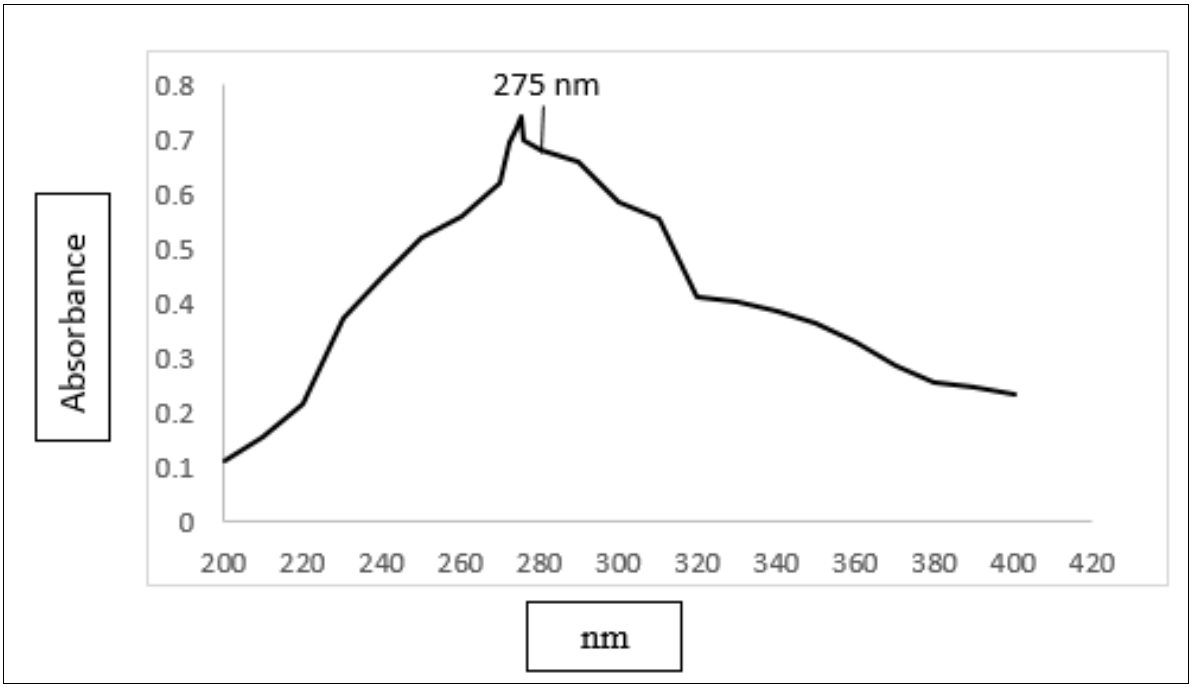

Fig 5: Determination of λ-max

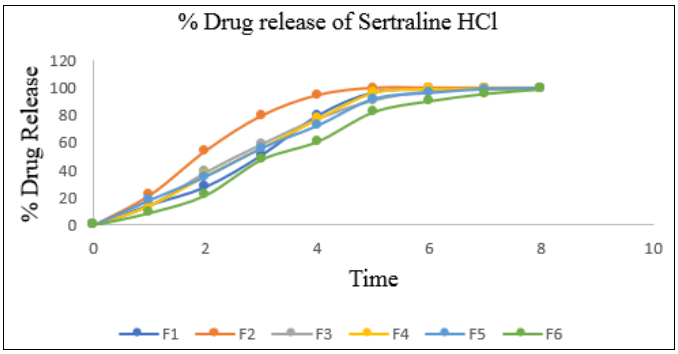

Fig 6: *In-vitro* Drug-release Profile of Sertraline HCl

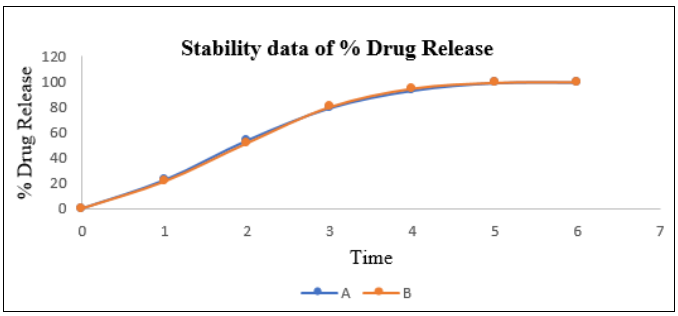

Fig 7: Stability data of % drug release

Conclusion

Preformulation parameters were performed and the result of angle of repose indicates free flowing characteristics of granules. From the FTIR, the interference was verified and found that Sertraline HCl did not interfere with the polymers and excipients used. Six batches of mouth dissolving tablets of Sertraline HCl were successfully prepared using drug-carrier complex, Camphor and Croscarmellose sodium by direct compression method and Sublimation technique. The evaluation of tablets was performed. *In vitro* release of formulation of MDTs tablets of F2 was found to be 99.68% drug release within 5 min with i*n-vitro* dispersion time being 26 sec. Based on the results, formulation F2 using combine approach of sublimating agent and superdisintegrants was identified as optimized MDTs formulation of Sertraline HCl. It appears that the use of superdisintegrants in higher concentration and camphor in lower concentration results in faster disintegration of the tablets with low friability. Camphor, used as sublimating agent, increases porosity of tablets due to which penetration of water takes place at high rate. This leads to faster disintegration of the tablets. Thus, it may be concluded here that the developed novel method for preparing MDTs of Sertraline HCl increases the porosity and enhances the bioavailability.

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