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FORMULATION AND EVALUATION OF MOUTH DISSOLVING TABLET OF SOLID DISPERSION BY SUBLIMATION TECHNIQUE

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ABSTRACT

The aim of the work was an attempt to make the formulation of mouth dissolving tablets by producing Pores in tablets by Sublimation technique, using subliming agents. Drug-carrier complex were prepared by solid dispersion solvent evaporation method of 1:3 ratio (Drug: carrier). Mouth Dissolving tablets of Sertraline HCl were punched by direct compression method. The compressed tablets are subjected to the process of sublimation in Hot air oven. All the formulated tablets were subjected for formulation evaluation parameters. 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. % friability of the tablet was less than 1. *In-vitro* dispersion time for tablets was in between 26- 47sec. *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. Among the all six formulations, the formulation containing 5mg of camphor and 5mg of croscarmellose sodium (F2) showed highest drug release in short time. For this study we can make conclude that the developed novel method for preparing MDTs of Sertraline HCl increases the porosity and enhances the bioavailability.

KEYWORDS

Mouth dissolving tablets (MDTs), Solid Dispersion, Direct compression, Super disintegrants, Sublimation techniques and Evaluation parameters.

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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 dosage forms used most commonly. 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]

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

Limitations of MDTs[5]

- Mechanical strength of the final product.
- Stability is formed by drug and dosage.
- Dissolution rate of the formulation of drugs in saliva.
- Swallow ability and mouth feel.
- The rate of absorption in saliva solution.
- Bioavailability overall.
- Dryness of the mouth may not be good candidates for these tablet formulations due to reduced saliva production.

MATERIAL 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[6]

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[7]

The drug-carrier complex, diluents super disintegrants, 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^{o}C for 6h.

Spectroscopic studies[8]

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 scanning range of solution was 200-400nm.

Standard calibration curve of sertraline HCl

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

Preparation of standard stock solution B (50µg/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 50µg/ml. Into a series of 10ml volumetric flasks, aliquots of second standard solution 1ml, 2ml, 3ml, 4ml, 5ml and 6ml was added and the volume made up to 10ml using pH 6.8 phosphate buffer. The absorbance of these solutions was measured against reagent blank at 275nm using Shimadzu (UV-1201) UV spectrophotometer. Standard curve was drawn

and x-axis indicates concentration and y-axis indicates absorbance.

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, drug and polymers physical mixture was taken.

CHARACTERIZATION OF BLENDS[9]

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. The below mentioned formula used for the calculation of bulk density.

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 measured in g/ml

Dt = M / Vt

Angle of repose (Ɵ)

The brim was filled by funnel and under gravity the test sample was subjected to flow smoothly through the orifice. To measure the area of pile, cone form taken on graph sheet. There by flow ability of the granules and height of the pile was evaluated.

$Ɵ = \tan^{-1}$ (h/r)

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[10-15]

Hardness Test

It is a force required to crush 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 centimetresquare (Kg/cm^2).

Friability Test

Friability is nothing but loss of weight of tablet in the container, because of removal of fine particles from the surface. Permitted friability limit is 1.0%. Roche Friabilator (Electro lab, Mumbai). The weighed ten tablets are placed in the friabilator chamber. In the friabilator, the tablets were subjected to rolling, finally free fall of tablets (6 inches) inside the friabilator chamber. The rotation speed of rate was 25rpm. Tablets were taken out from the friabilator after 100 rotations and by collectively again weighed intact tablets.

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

Weight Uniformity Test

Fifteen tablets were weighed individually. The average weight and individual weight comparison were takes place. The weight variation % difference should not cross the permissible limits (±7.5%). 200mg was the total weight of the formulated tablet.

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 1000mcg/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

The strength to with stand compression force applied during manufacturing process was indicated by the thickness of the tablets. Digital caliper was used for the measurement of thickness of tablets.

***In-vitro* dispersion Time**

In vitro dispersion time was measured by dropping a tablet into a Petri dish containing 10ml 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 10cm 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. The complete tablet should not immerse in the solution when a tablet is kept on the surface of the tissue paper. Then, the time required for buffer to reach upper surface of the tablet is noted as wetting time.

***In vitro* disintegration time**

The determination of disintegration time was done by 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 study of the samples was done by using USP - type II dissolution apparatus (paddle type). 900ml of phosphate buffer (pH 6.8) dissolution medium solution was used and placed into the dissolution flask. The flask must have the temperature of 37±0.5ºC and rpm of 50. In dissolution apparatus each flask contains single tablet and subjected to run for 10 min. Samples measuring 5ml were withdrawn after every 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10min. Samples were filtered through 10µm filter. The sink condition was maintained by replacing the fresh dissolution medium in every time of sample collection. The collected samples were analysed at 275nm using dissolution medium as blank. The percentage drug release was calculated.

Stability study[16]

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 coloured 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.

RESULTS 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 No.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 release di.e., 99.68% of the drug with in 5min.

Table No.1: Formulation Design for the preparation of MDTs

S.No	Ingredients	F1	F2	F3	F4	F5	F6
1	drug-carrier complex (eq. to 25mg of drug) (mg)	100	100	100	100	100	100
2	Croscarmellose sodium	4	5	4	5	4	5
3	Camphor	5	5	10	10	15	15
4	Sucralose	2	2	2	2	2	2
5	Magnesium stearate	1	1	1	1	1	1
6	Talc	1	1	1	1	1	1
7	Mannitol	62	61	57	58	52	51
8	Total weight	175	175	175	175	175	175

Table No.2: Precompression parameters of Sertraline hydrochloride tablet

S.No	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 (%)
1	F1	2.56±0.12	0.54	2.59±0.03	27±1.6	25±2.3	29±2.4	0.55	99.32
2	F2	2.52±0.28	0.54	2.56±0.02	24±1.8	23±1.8	26±1.5	0.81	98.52
3	F3	2.71±0.12	0.57	2.67±0.10	31±1.4	29±1.2	35±3.4	0.78	99.06
4	F4	2.64±0.24	0.62	2.74±0.15	35±2.1	33±3.2	38±1.7	0.72	99.19
5	F5	2.9±0.36	0.64	2.65±0.01	39±2.8	37±2.2	44±2.5	0.86	97.72
6	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 No.3: Post-compression parameters of Sertraline HCl tablet

S.No	Formulation code	F1	F2	F3	F4	F5	F6
1	Angle of repose (Ɵ)	23.82	23.24	25.66	25.01	24.35	26.10
2	Bulk density (g/cc)	0.53	0.51	0.56	0.52	0.55	0.54
3	Tapped density(g/cc)	0.64	0.67	0.69	0.65	0.68	0.66
4	Carr's index (Carr, Jr)	13.72	15.26	19.35	14.61	18.51	14.63
5	Hausner's ratio	1.14	1.27	1.12	1.23	1.15	1.24

Table No.4: Tablet weight (mg) before and after sublimation of camphor

S.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 No.5: Data for calibration curve of Sertraline HCl at 275nm

S.No	Time	% drug release					
		F1	F2	F3	F4	F5	F6
1	00	0	0	0	0	0	0
2	01	14.75	21.85	14.30	14.28	18.27	8.98
3	02	28.02	54.11	38.39	35.89	35.35	21.88
4	03	51.14	79.58	58.76	56.16	56.00	47.78
5	04	79.95	94.43	77.14	77.21	72.30	60.98
6	05	96.90	99.68	90.49	96.36	91.66	82.46
7	06	98.99	99.68	97.26	99.14	95.94	90.42

Table No.6: *In-vitro* Drug-release Profile of Sertraline HCl

S.No	Formulation code	Camphor (mg)	Sublimation (mg)	
			Before	After
1	F1	5	175.5	171.4
2	F2	5	175.2	171.4
3	F3	10	175.0	166.5
4	F4	10	175.1	166.6
5	F5	15	175.2	161.0
6	F6	15	175.2	161.2

Table No.7: Stability data of the Sertraline HCl MDTs formulation F2

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

Table No.8: Stability data of % drug release study

S.No	Time (min)	% drug release	
		A	B
1	1	22.53	21.37
2	2	53.86	51.73
3	3	79.34	80.11
4	4	93.11	94.65
5	5	99.06	99.22
6	6	99.56	99.68

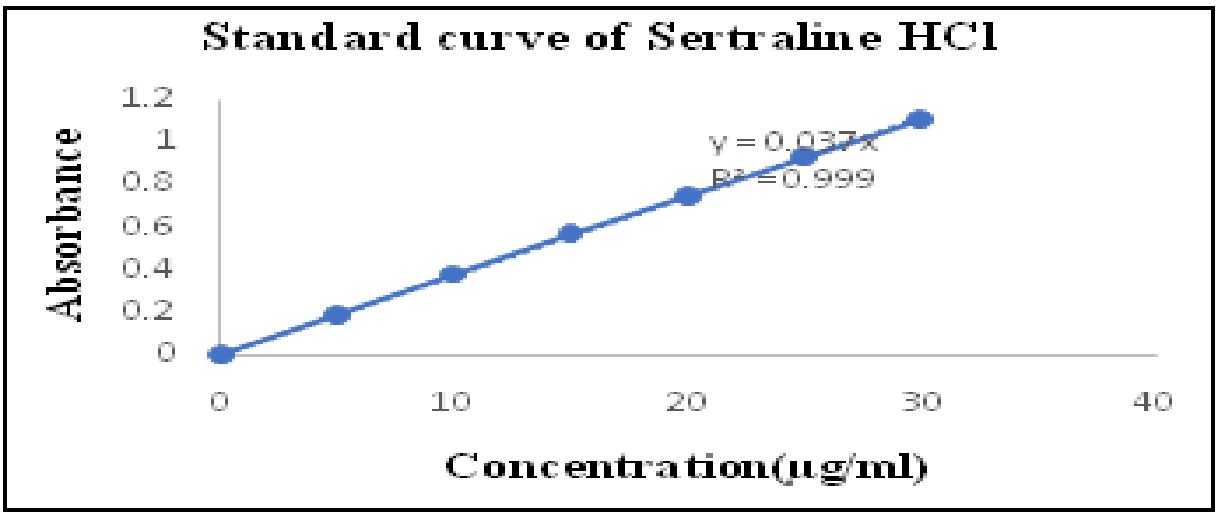

Figure No.1: Standard calibration curve of Sertraline HCl

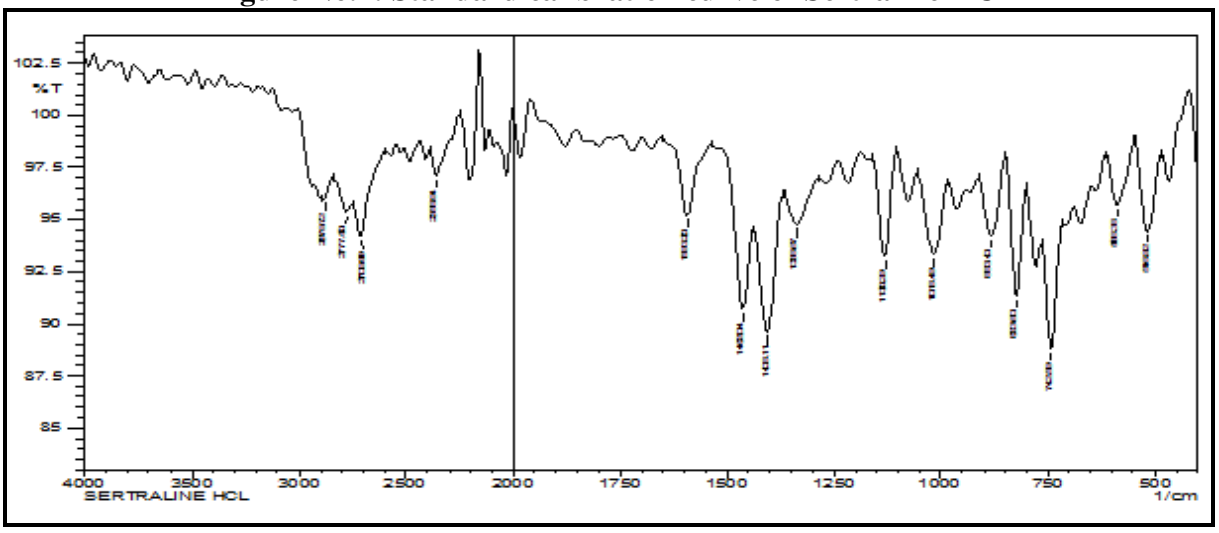

Figure No.2: FTIR Spectra of Sertraline HCl

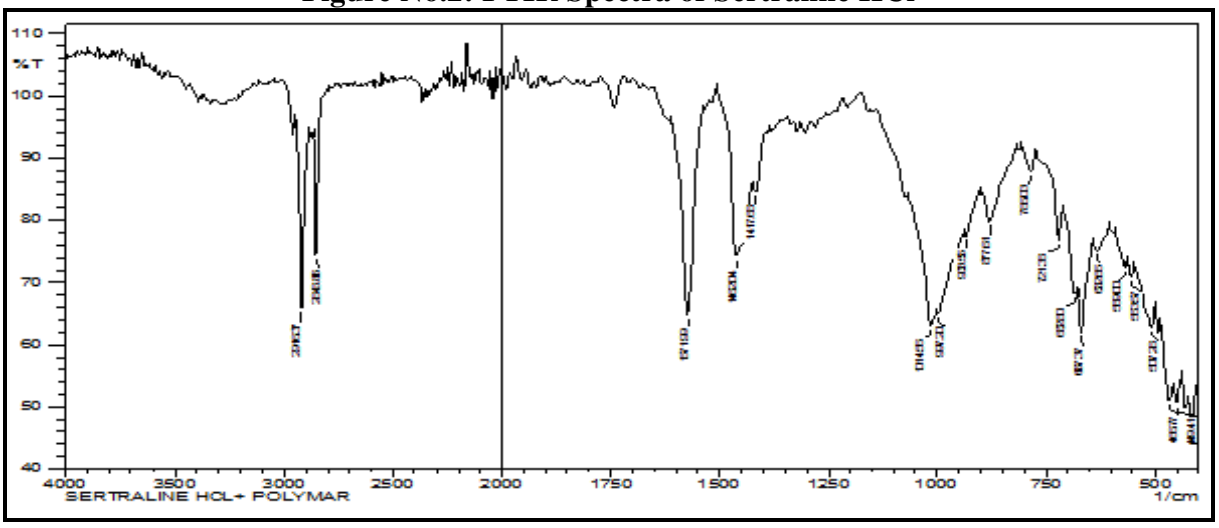

Figure No.3: Sertraline HCl + HPβCD Complex

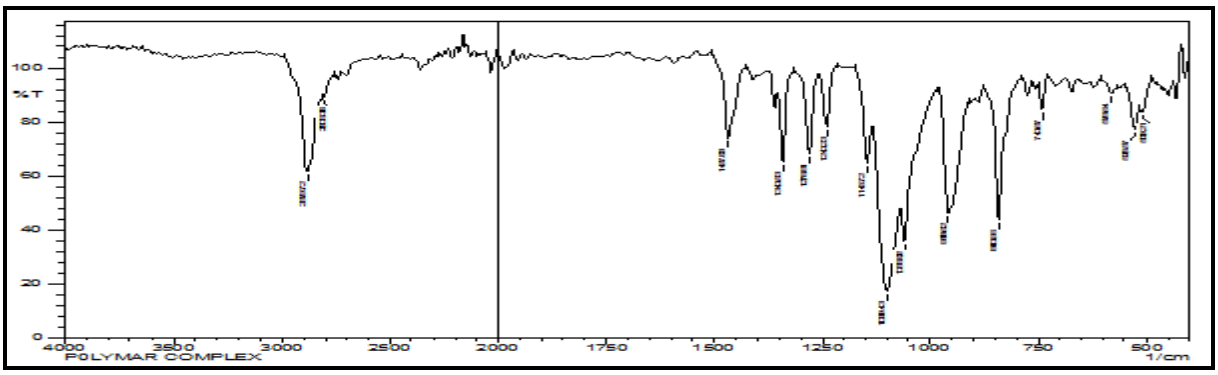

Figure No.4: Sertraline HCl + HPβCD + Excipients

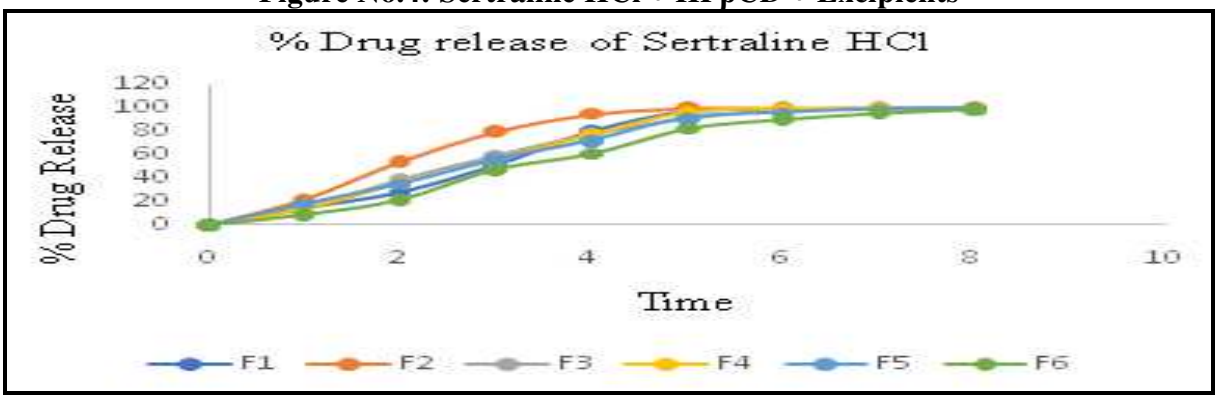

Figure No.5: Determination of λ-max

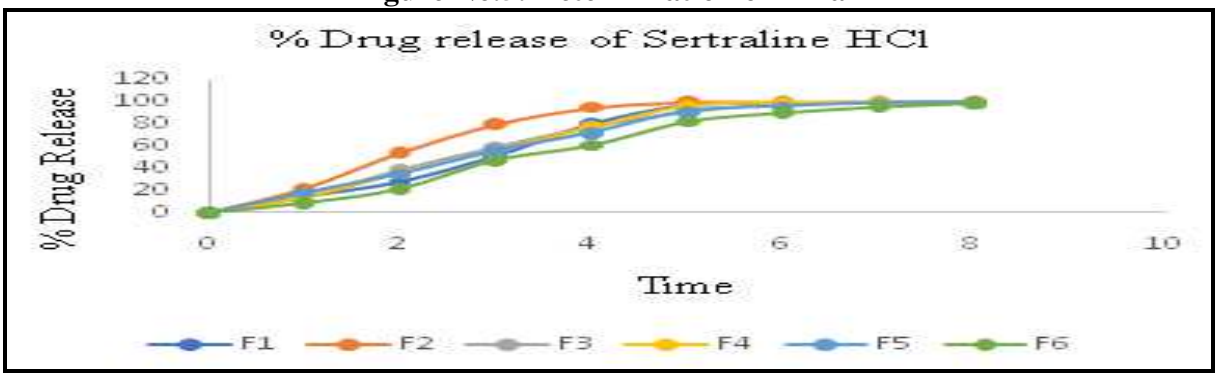

Figure No.6: *In-vitro* Drug-release Profile of Sertraline HCl

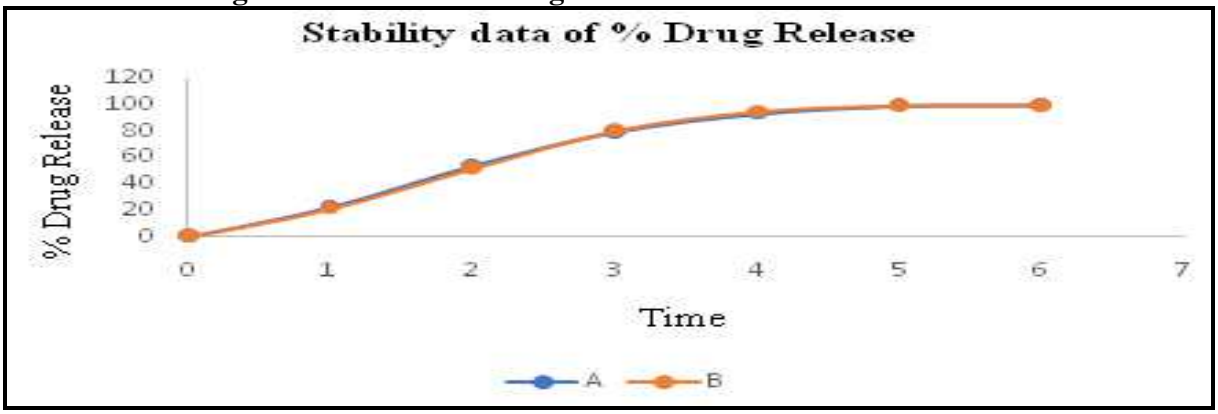

Figure No.7: Stability data of % drug release

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 per formed. *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 super disintegrants was identified as optimized MDTs formulation of Sertraline HCl. It appears that the use of super disintegrants 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. For this study we can make conclude that the developed novel method for preparing MDTs of Sertraline HCl increases the porosity and enhances the bioavailability.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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