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Formulation and evaluation of serratiopeptidase and salbutamol tablet for dysphagia

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***Abstract*---**Oral Dispersible Tablet of Serratiopeptidase and salbutamol were prepared, evaluated and different types of concentration and dissolution of tablets were studied. In FTIR, drug and excipients with their mixture showed that there is no interaction between the drug molecule and excipients used. The Percentage of drug content of tablets in the formulations was found to be 95 % to 105% which complies with the limits of pharmacopoeia. By the process of direct compression method was used to prepare oral Dispersible tablet containing 300 mg of Serratiopeptidase and salbutamol. formulation was conducted using different concentrations of croscarmellose, micro crystalline cellulose, as a super disintegrants. And their interaction with Serratiopeptidase and salbutamol also evaluated using FTIR.

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Keywords---fast dissolving tablets, mouth dissolving tablets, orally disintegrating tablets.

Introduction

Oral Dispersible Tablets are a type of tablet that dissolves when it comes into contact with saliva. The drug is released from the dosage form as a result of this. Super disintegrants like croscarmellose can increase the disintegration of tablets in the oral cavity, making the dosage form acceptable for youngsters, the elderly, bedridden patients, and dysphagia sufferers. The United States Food and Drug Administration defines an oral dispersible tablet as "a solid substance or active component that is easily dispersible when the tablet is placed on the tongue and should disintegrate within a few seconds." The oral tablet is also known as a rapid disintegrating tablet, a mouth dissolving tablet, a fast-dissolving tablet, and a quick dissolving tablet. This dosage form is widely used in children's, the patients who have difficulties in swallowing in case of Dysphagia, Bedridden patients. Or Psychiatric patients.

Serratiopeptidase it is the proteolytic enzyme, that is used to be reduce the inflammation i.e. it works as anti-inflammatory and analgesic agent. Serratiopeptidase is soluble in water and insoluble in alcohol. This proteolytic enzyme is quickly absorbed and delivered into the bloodstream through the colon. There are several issues with serratiopeptidase for oral delivery when there is a high chance of enzymatic breakdown in the GIT tract. Salbutamol is a beta2-adrenergic receptor agonist with a short half-life that is used to treat asthma and COPD. Bronchodilator is another name for it. Salbutamol dissolves quickly in water with no lag time. The focus of this research is to develop oral dispersible tablets containing serratiopeptidase and salbutamol in order to achieve quick dissolution, absorption, and increased drug bioavailability. Salbutamol and Serratiopeptidase oral dispersible tablets developed to improve patient compliance and give a faster onset of action.

Materials and Methods

Materials

Serratiopeptidase and Salbutamol were purchased from Arti distributor, Mumbai, India. Similarly Micro crystalline cellulose, Croscarmellose, Magnesium stearate and talc were obtained from pharmaceutical department.

Methods

DSC

Differential scanning calorimetry is the thermo-analytical techniques. Heat input or output of a sample was measured with the help of calorimeter. DSC thermograms of Serratiopeptidase and salbutamol were established by analysing the drug. The drug component was placed in an aluminium pan and subjected to DSC instrument (METTLER, STAReSW 12.10.) Indium was used as reference

standard. During heating the sample from 250^{0}C to 300^{0}C at a rate of 10oC/ min the DSC spectrum were recorded.

FTIR

Fourier Transform Infrared Spectroscopy was carried out for solid samples to identify the presence of various functional groups present in drug. The samples were prepared by the potassium bromide disc method. Powders (20mg drug in 280mg KBr) were triturated in agate mortar and pestle to produce fine and uniform mixture. Prepared sample disc was placed in a sample holder and transferred to sample compartment. Samples were scanned in the region of 4000-400 cm-1 using a Bruker FTIR spectrometer and it was compared with standard.

Preparation of Serratiopeptidase and Salbutamol Sulphate

Direct compression method was used to prepare oral dispersible tablet of Serratiopeptidase and salbutamol. At first all the ingredients excluding lubricant, glidant, sweetner and diluent (Micro crystalline cellulose) were passed through sieve and the remaining ingredients were passed through sieve of mesh size 50. Then all the ingredients except glidant and lubricant were weighed correctly and mixed thoroughly. Finally lubricant and glidant were added to the powder and mixed thoroughly to obtain uniform particle size. The prepared powder blend was then compressed with tablet compression machine using die of 7 mm diameter.

Formula

Table 1
Formulation of Serratiopeptidase and Salbutamol ODT

Ingredients	F1	F 2	F 3	F 4
Serratiopeptidase	80	80	80	80
Salbutamol	10	10	10	10
Croscarmellose	*40*	*45*	*55*	*60*
Mg. Stearate	30	30	30	30
MCC	*120*	*115*	*110*	*105*
Talc	20	20	20	20

#Total tablet– 300mg

Evaluation of pre-compression flow properties of powder blend
Organoleptic properties

Organoleptic properties of drug like colour, odour and solubility were observed and recorded. Solubility was observed in Water and Ethanol.

Bulk Density

Bulk density was measured using bulk density apparatus. Fixed weight of powder was poured in the measuring cylinder and volume was recorded.
Bulk density = Bulk weight/Bulk volume

Tapped Density

Fixed weight of powder was poured in the measuring cylinder and tapped 50 cycles multiple times. Volume was recorded after each 50 tapping cycles until fixed (concurrent) reading was obtained. The tapped density was obtained by using following equation:
Tapped Density = Bulk weight/Tapped volume

Carr's Index

Carr's index was obtained by using following equation:
Carr's index (%) = $\frac{\text{tapped density}-\text{bulk density}}{Tapped\ Density} \cdot X100$

Tapped density Value less than 1.25 indicate good flow (=20% Carr), where greater than 1.25 indicates poor flow.

Angle of Repose

Fixed weight of powder was poured through funnel. The height and diameter of the power pile was noted. Angle of repose was obtained by using following equation:

Angle of repose $\theta = tan^{-1}(2h/d)$

Where, h = maximum height

D = Average diameter

Hausner's ratio

Flow properties of the powder can also be examined using hausner's ratio. Hausner's ratio was obtained by using following equation:

$$\text{Hausner's ratio} == \frac{\text{Tapped Density}}{Bulk\ Density}$$

The value of ratio below 1.25 indicates good flow while above 1.35 indicates the poor flow

Post Compression Studies
Weight variation

For each batch, 20 tablets were taken and weighed for weight of each tablet using a digital balance. The average weight of tablet for was determined and minimum and maximum deviation was calculated for each batch.

Thickness

Dimension of 10 tablets for each batch was determined using vernier caliper and the average diameter and thickness was determined.

Hardness

Using Monsanto Hardness tester, the hardness of 10 tablets was measured and average hardness of tablets was determined.

Friability

The weight of tablets equal to 6.5 grams were taken and rotated for 100 cycles in a friabilator. After 100 revolutions, the tablets were weighed and percentage loss was calculated.

Dissolution Test

The in-vitro dissolution study was carried out with the USP dissolution test apparatus.900ml of dissolution medium (6.8 phosphate buffer) was taken in covered vessel and the temperature was maintain at 37 ± 0.5 ^{0} C. The speed of the paddle was set at 100rpm.Sampling was done every 10min interval. For each sample 10ml of dissolution medium was withdrawn and the same amount of dissolution medium at 37oC was replaced. The sample withdrawn was filtered with what man filter paper and diluted with 6.8 phosphate buffer and then analysed in the UVspectrophotometer. The absorbance was measured at 660nm and percentage drug release was calculated.

Disintegration test

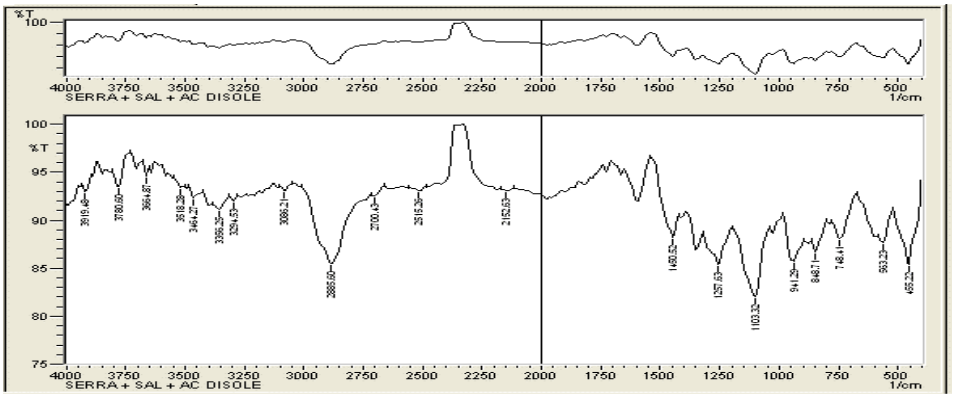
For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration. This is one of the important quality control tests for disintegrating type tablets. Six tablets are tested for disintegration time using USP XXII apparatus. Disintegration type sustained release tablets are tested for disintegrating time.

Results and Discussion

FTIR

FTIR studies were done to evaluate whether there is any interaction between the active ingredient serratiopeptidase and salbutamol and the excipients used in the formulations. The peaks of the active ingredient serratiopeptidase and salbutamol with the mixture of excipients with one another, the peaks positions are at the same wave number, Serrratiopeptidase + salbutamol + AC DI SOLE
The FT-IR Spectroscopy Was done and following spectra were observed.

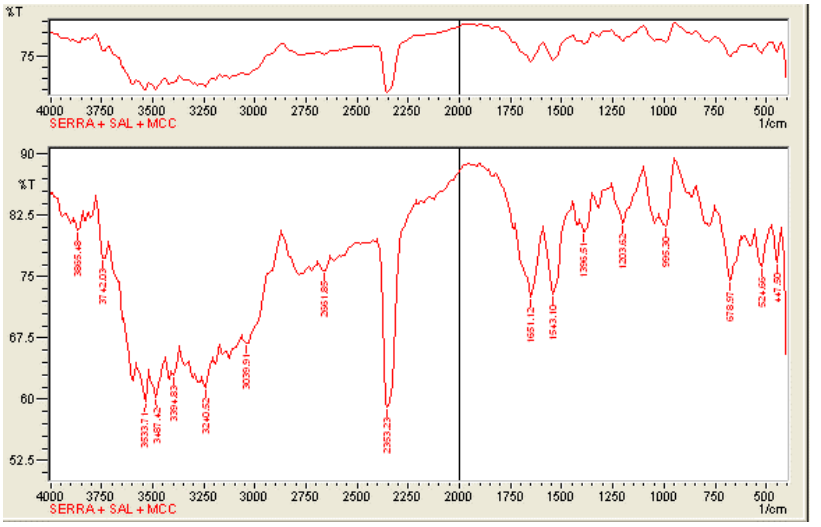
Serratiopeptidase + Salbutamol + AC DI Sole



Graph :- FTIR spectra of mixture of Serratiopeptidase + Salbutamol + AC DI Sole

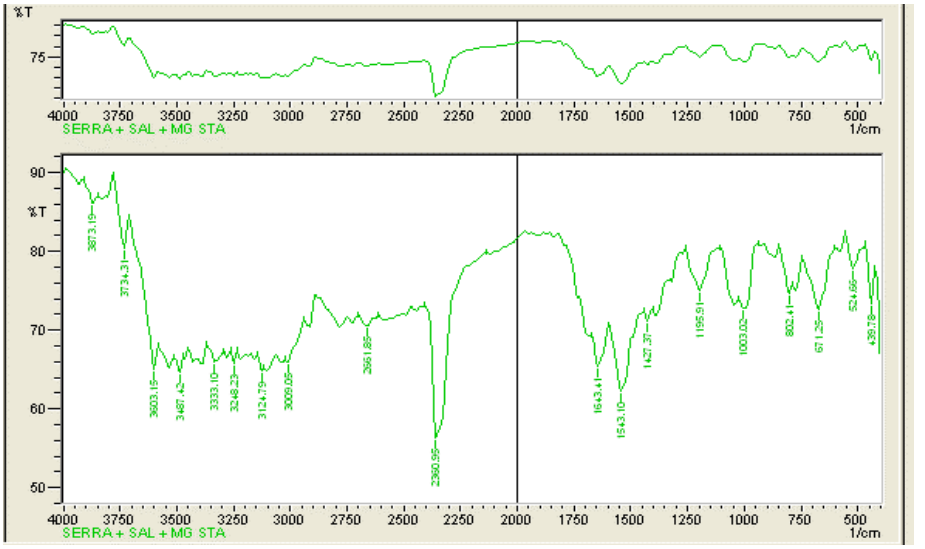
Observation: Identification and Confirmation of active pharmaceutical ingredients was carried by observing the FT-IR Spectra. Mixture of Serratiopeptidase + Salbutamol+ Ac DI Sole Showed characteristics peak at Values 3294.53(=O-H Stretching);2885.60(=N-H Stretching);2700.43(=O-H Stretching);1103.32(=C-O Stretching);1257.63(=C-H Stretching)

Serratiopeptidase + salbutamol+Mcc



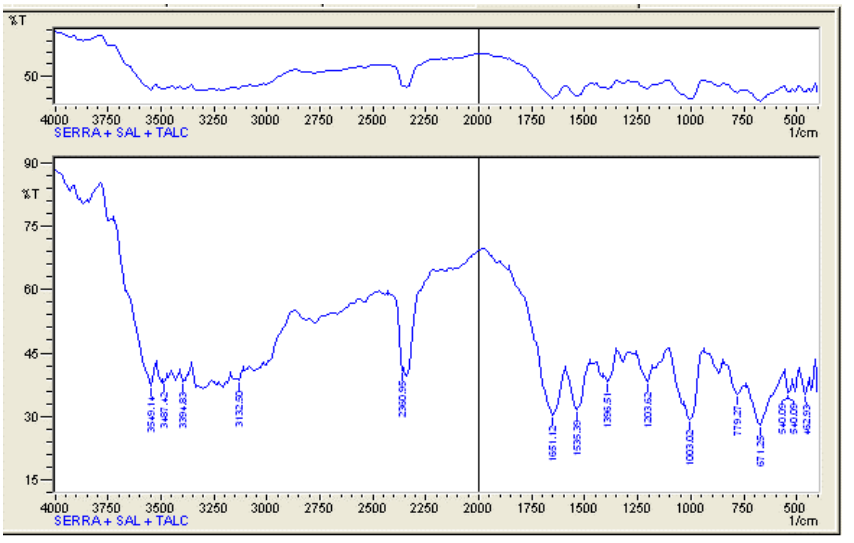
Observation: Mixture of Serratiopeptidase + Salbutamol + MCC Showed characteristics peak at values 3394.83(=N-H Stretching);3533.71(=O-H Stretching);1651.12(=C-C Stretching);1543.10(=N-O Stretching);3039(=O-H Stretching).

Serratiopeptidase + Salbutamol + Mg. Stearate



Observation: Mixture of Serratiopeptidase + Salbutamol + Mg. Stearate Showed Characteristics peak at values 3603.15(=O-H Stretching);2661.85(=C-H Stretching);1543.10(=N-O Stretching);1195.91(=C-O Stretching) 2533.23 (=N=C=O Stretching)

Serratiopeptidase + Salbutamol + Talc

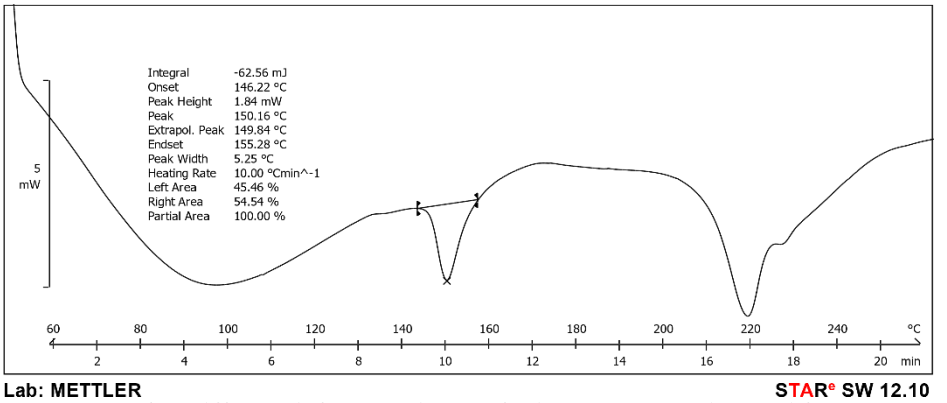


Observation: Mixture of Serratiopeptidase + salbutamol + Talc showed characteristics peak at values 3549.14(=O-H Stretching);3394.83(=N-H Stretching);3132.50(=O-H Stretching);1535.39(=N-O Stretching);1203.62(=C-O-Stretching).

DSC (Differential Scanning Calorimetry)

Sample A:- Serratiopeptidase

The Melting Point of Serratiopeptidase is 146^{0}C -148^{0}C

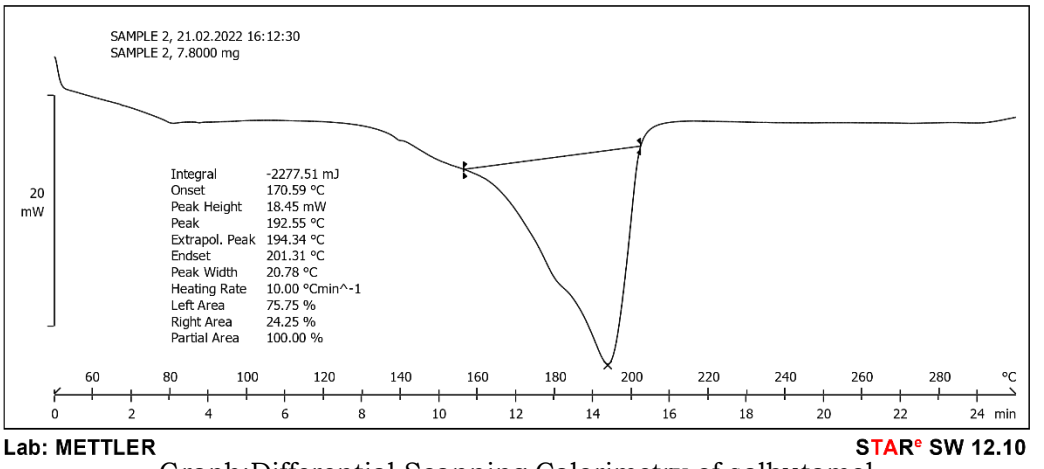


Graph: Differential Scanning Calorimetry Serratiopeptidase

A Curve is observed in the graph. The onset temperature is 146.22^{0}C and the peak transition temperature is 150.16^{0}C that is the melting point of Serratiopeptidase. So, the thermal identification of Serratiopeptidase is done with the help of DSC.

Sample B: - Salbutamol

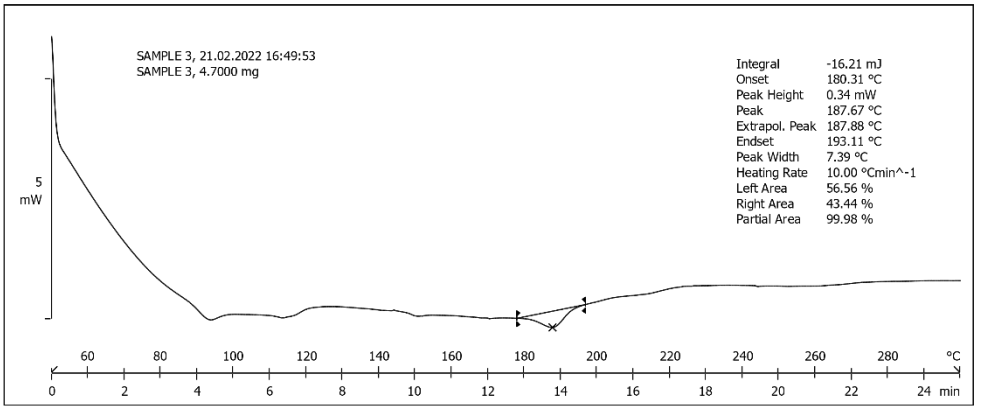
The Melting Point of Salbutamol 170^{0}C – 180^{0}C



Graph:Differential Scanning Calorimetry of salbutamol

A Curve is observed in the graph. The onset temperature is 170.59^{0}C and the peak transition temperature is 192.55^{0}C that is the melting point of Salbutamol. So, the thermal identification of Salbutamol is done with the help of DSC.

Sample C: - Mixture (Serratiopeptidase and Salbutamol)

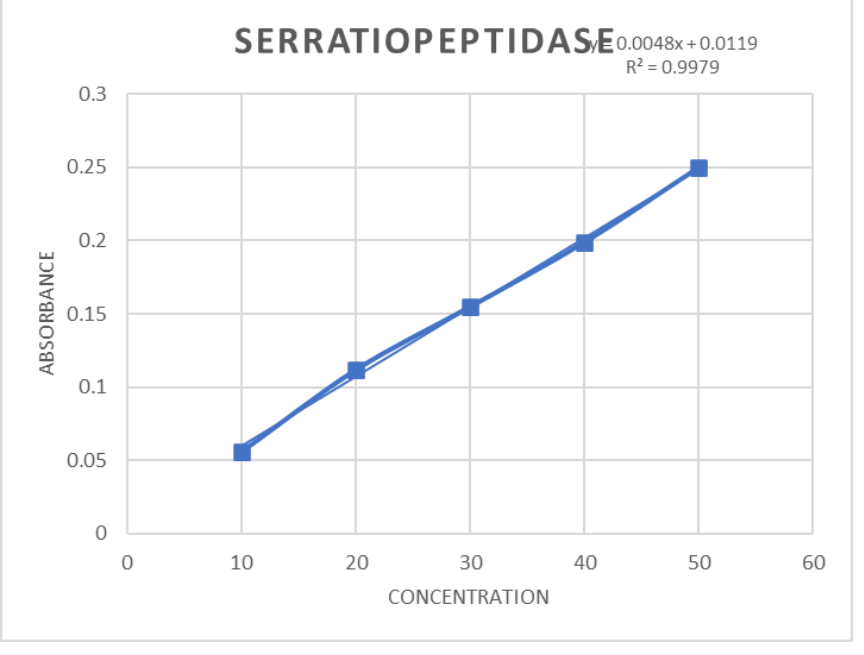


Graph: Differential Scanning Calorimetry of Serratiopeptidase and salbutamol combination

A curve is observed is on the graph. The onset temperature is 180.31 ^{0}C. It Shows the melting point of salbutamol, so the combination shows compatibility so the thermal compatibility of this combination is done with the help of DSC.

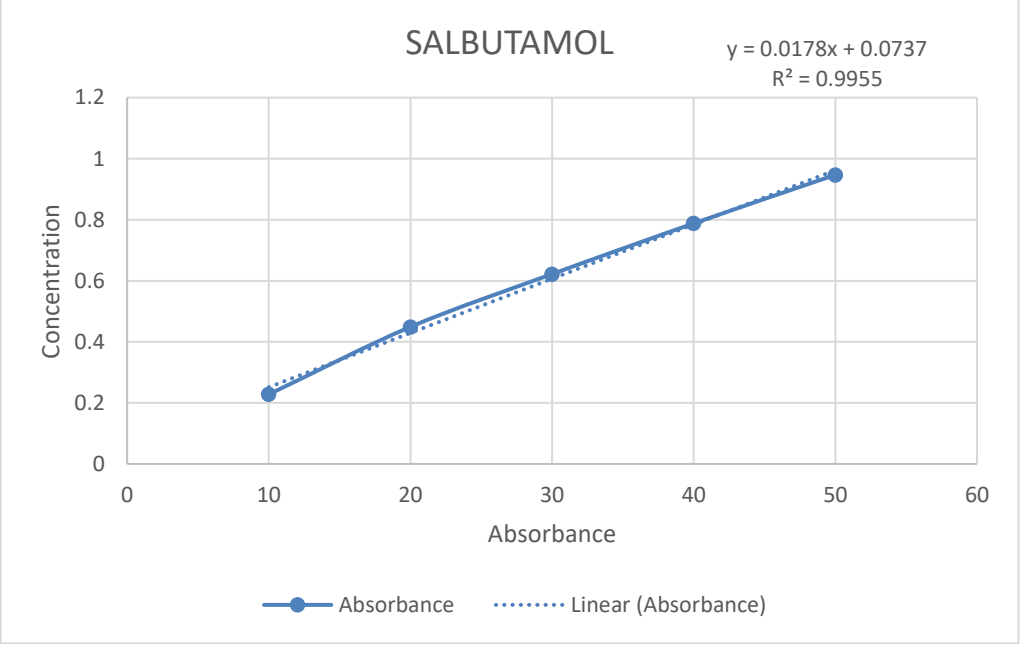
Standard Graph of Serratiopeptidase

When absorbance v/s concentration was plotted, a straight line was obtained which suggests that the process used to measure the absorbance of sample is validated.



Concentration(µg/ml)	Absorbance
10	0.059
20	0.112
30	0.155
40	0.199
50	0.250

Standard Graph of Salbutamol



Concentration(µg/ml)	Absorbance
10	0.228
20	0.449
30	0.622
40	0.788
50	0.947

General appearance

Visual observation revealed that all the tablets of four formulations were round.

Table 2
Formulation Table for Post Compression Studies

Batch	Weight Variation	Thickness	Hardness	Friability	Disintegration Time
F1	0.112	3.1	3.3	0.21	4m30sec
F2	0.121	3.3	3.5	0.33	5m20sec
F3	0.13	3.2	3.1	0.38	3m50sec
F4	0.129	3.1	3.4	0.45	6m10sec

Physical Parameters

Formulation	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Angle of Repose	Carr's Index (%)	Hausners Ratio (HR)
F1	0.4247	0.5135	26.15	17.29	1.20
F2	0.3903	0.5448	26.95	30.08	1.40
F3	0.3563	0.5270	25.70	32.39	1.47
F4	0.4159	0.5150	25.34	19.24	1.23

Pre-Compression Study

Table 3
Formulation Table for Pre-Compression Studies

Wavelength 276 Nm	F 1	F 2	F 3	F 4
5 Min	0.012	0.004	0.006	0.009
15 Min	0.0128	0.006	0.012	0.015
30 Min	0.013	0.0087	0.0178	0.025
45 Min	0.0145	0.0115	0.0205	0.0268
60 Min	0.0149	0.0138	0.0235	0.0299

Comparative Dissolution profile of formulations.

Table 4
Formulation table for Dissolution Study.

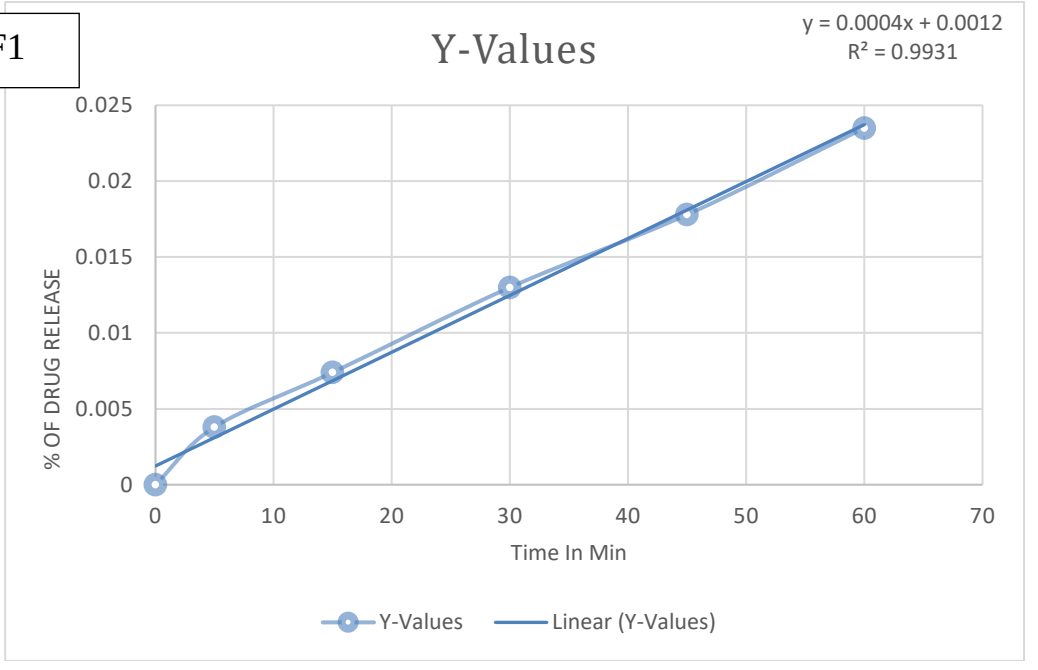
Sr No	Time	Absorbance
1	0	0
2	5	0.0038
3	15	0.0074
4	30	0.013
5	45	0.0178
6	60	0.0235

Sr.no	Time (Min)	Absorbance
1	0	0
2.	5	0.005
3.	15	0.0021
4.	30	0.0087
5.	45	0.0113
6.	60	0.0158

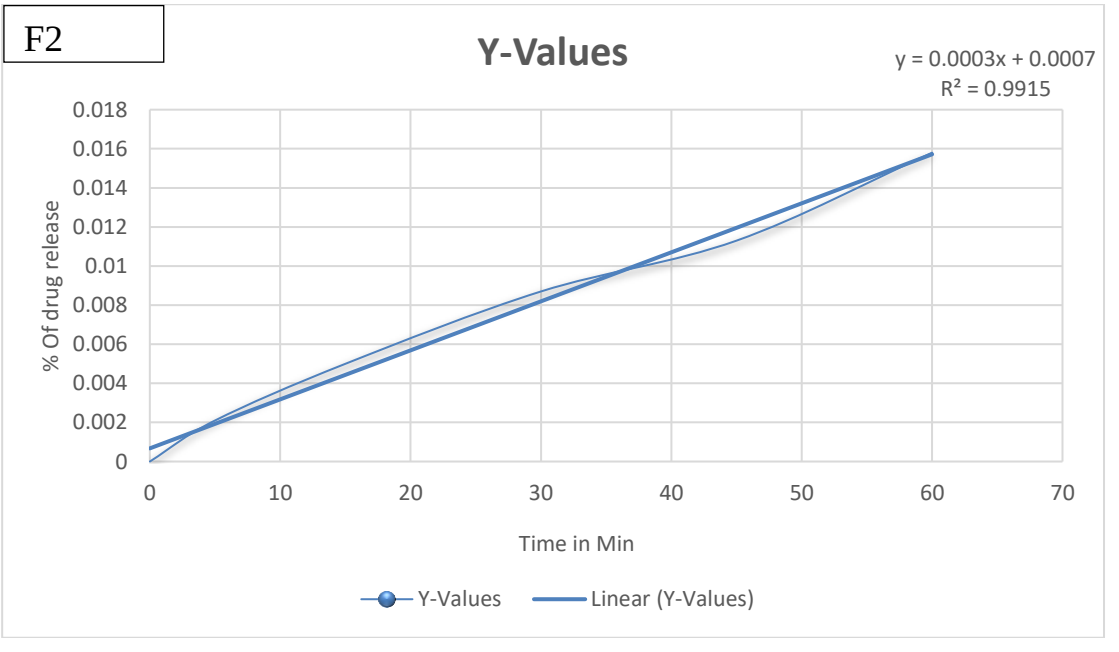
Sr.no	Time (Min)	Absorbance
1.	0	0
2.	5	0.004
3.	15	0.009
4.	30	0.0149
5.	45	0.0215
6.	60	0.0275

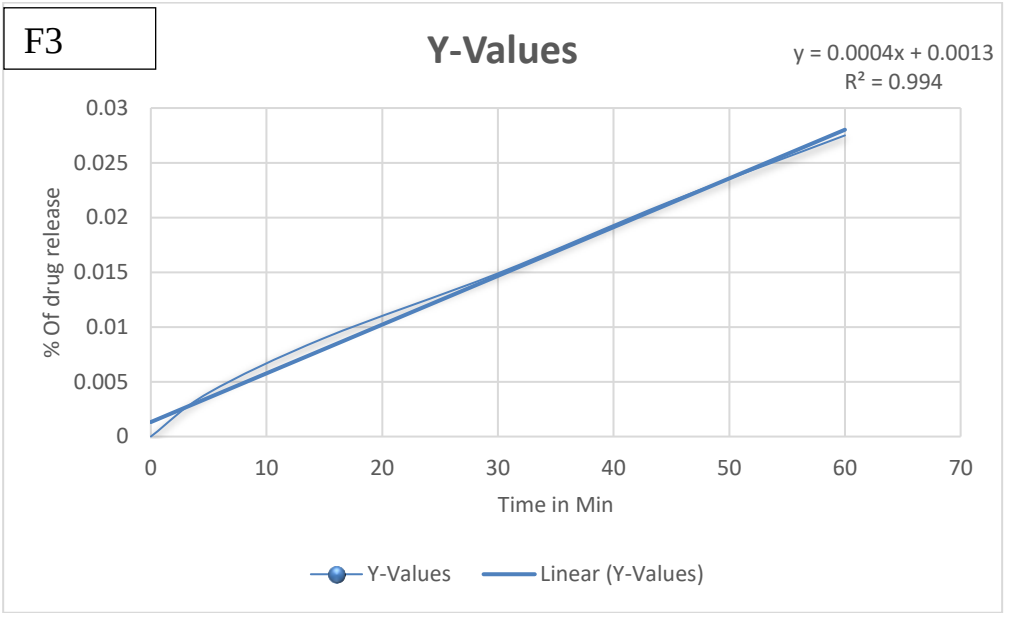
Sr.no	Time (Min)	Absorbance
1	0	0
2	5	0.0052
3	15	0.0103
4	30	0.0175
5	45	0.0255
6	60	0.0326

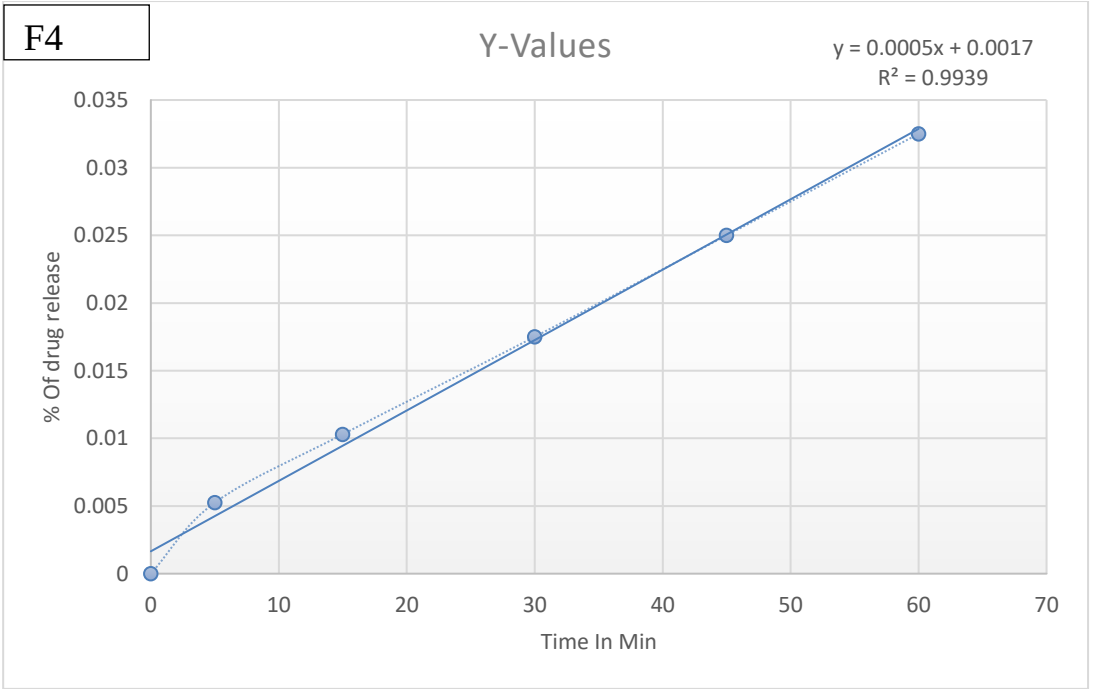
F1


Y-Values
y = 0.0004x + 0.0012
R² = 0.9931
% OF DRUG RELEASE
0.025
0.02
0.015
0.01
0.005
0
0
10
20
30
40
50
60
70
Time In Min
Y-Values
Linear (Y-Values)

F2


Y-Values
y = 0.0003x + 0.0007
R² = 0.9915
% Of drug release
0.018
0.016
0.014
0.012
0.01
0.008
0.006
0.004
0.002
0
0
10
20
30
40
50
60
70
Time in Min
Y-Values
Linear (Y-Values)





Discussion

IR spectrum of Serratiopeptidase sample was interpreted. From these, we can say that the given sample may be Serratiopeptidase. The oral dispersible of Serratiopeptidase and salbutamol were formulated and evaluated. The use of super disintegrants for the formulation of the ODTs was satisfactory and commercially feasible. The use of super disintegrants caused quick disintegration

and prompt dissolution of the tablet. The FTIR study of the drug molecule and its mixture with the excipients were performed to show the compatibility of the drug molecule and the excipients. The FTIR peak corelates with the mixture to show that there is no interaction between component.By using Super disintegrants, they show better results in case of hardness, disintegration, etc. All the tablets passed the weight variation test as the percentage weight variation was within USP limits. The hardness of the tablets was in between 3.1 to 3.5 kg/cm2. The friability of the tablets was in between 0.21% to 0.45%. The disintegration time of the formulated batches was between 4 min 30sec to 6 min 10 Sec.

Conclusion

The oral Dispersible tablet of Serratiopeptidase and salbutamol were prepared successfully by the use of direct compression method. Different formulations were designed to evaluate the influence of different concentrations of super disintegrants on ODTs of Serratiopeptidase and salbutamol. Four formulations with different concentrations of super disintegrants were prepared. FTIR studies using the drug and its mixtures with the excipients showed that the peaks correlate with one another which signify that there is no interaction between the drug molecule and the excipients used. This suggests that the composition of Serratiopeptidase and salbutamol ODTs could be optimized so as to obtain rapid disintegration and drug dissolution along with acceptable tablets hardness and friability. This could be helpful to improve the drug's absorption and bioavailability, which helps to better patient compliance and convenience.

Conflict of Interest

None declared by the authors.

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