To Formulate And Evaluate Sustained Release Matrix Tablet Of Salbutamol Sulphate From Tamarind Seed Polysaccharide As A Release Retarding Agent

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Abstract: This study examines the sustained release behavior of salbutamol sulphate from tamarind seed polysaccharide isolated from tamarind kernel powder. Salbutamol sulphate is an antiasthamatic and bronchodilator agent with half-life of 1.6 hours and requires multiple daily doses to maintain adequate plasma concentration. Hence present study was undertaken with an aim to formulate and evaluate sustained release matrix tablet of salbutamol sulphate from tamarind seed polysaccharide as a release retarding agent. FT-IR studies revealed that there was no interaction between the drug and polymers used in the study. All lubricated formulations were compressed by direct compression. The compressed tablets were evaluated for uniformity of weight, content of active ingredient, friability, hardness, thickness, in vitro dissolution and stability study. Release studies were carried out using USP type 2 apparatus in 900 ml of distilled water as dissolution media. Release kinetics were analyzed using zero-order, Higuchi's square root and Peppas' exponential equations. All formulations showed compliance with pharmacopoeial standards. Among different formulations F5 and F6 showed sustained release of drug for 12 hours with 97.89% and 90.59% of drug release respectively. The regression coefficient value of zero order plots was found to be 0.983 and 0.952 for F5 and F6 respectively. The slope of peppas equation was found to be 0.769 for F5 and 0.704 for F6 indicating drug was released by non-fickian diffusion release mechanism. Thus isolated TSP was found to be effective in retarding release of salbutamol sulphate.

I. AIM

The aim of present study is to develop sustained release matrix tablets of salbutamol sulphate which releases the drug in a sustained manner over a period of 12 hours, by using Tamarind seed polysaccharide (TSP) and study effects of TSP concentration on release pattern.

OBJECTIVES

- ✓ Isolation of tamarind seed polysaccharide from tamarind kernel power
- ✓ Characterization of isolated tamarind seed polysaccharide

- ✓ To formulate the sustained release tablet of Salbutamol sulphate from To study the effect of Tamarind seed polysaccharide concentration on tablet characteristic.
- ✓ Maximum utilization of drug with minimum side effects
- ✓ To improve patients compliance

II. MATERIALS AND METHOD

LIST OF MATERIALS & EQUIPMENTS

Sr. No.	Materials	Property	Source
1	Salbutamol sulphate	Pure drug	Laben pharmaceuticals, Akola

2	Tamarind seed polysaccharide	Polymer	Tamarind kernel industry, Bizapur.
3	Microcrystalline cellulose	Diluent	SDFCL, Mumbai
4	Magnesium stearate	Lubricant	S.D fine, Mumbai
5	Talc	Glidant	S.D fine, Mumbai

Table 1: Procurement of drug and Excipients

Sr.No.	Instrument	Manufacturer
1.	Digital Balance	Citizen
2.	U.V.Spectrophotometer	Shimadzu 1800
3.	Tablet Compression machine	KarnavatiRimek mini press 1
4.	Dissolution test apparatus	Electro lab (8 station)
5.	Friabilator	Labline
6.	Hardness	Monsanto Hardness tester
7.	Thickness	Vernier caliper
8.	P^H meter	Equip-tronics
9.	Viscometer	Brookfield DV-1 Prime
10.	FTIR	Perkin Elmer Spectrum 100

Table 2: List of Equipments and manufacturer

PREFORMULATION STUDY

Almost all the drugs which are active orally are marketed as tablets, capsules or both. Prior to development of dosage forms with a new drug candidate, it is essential that certain fundamental physical and chemical properties of the drug molecule and other derived properties of the drug powder are determined. The information will dictate many of the subsequent events and possible approaches in formulation development.

METHOD OF ISOLATION OF TSP

The alcohol-insoluble fraction from the water extract of tamarind seed meal, constituting 60 to 65 per cent of the husked kernel, has been described as a rich source of polysaccharides. TSP was prepared following methods by Rao et al., in three batches on a laboratory scale. 20 g of tamarind kernel powder was added to 200 ml of cold distilled water to prepare slurry. The slurry was poured into 800 ml of boiling distilled water. The solution was boiled for 20 min with continuous stirring. The resulting solution was kept overnight and centrifuged at 5000 rpm for 20 min. The supernatant liquid was separated and poured into twice the volume of absolute alcohol with continuous stirring. The product was pressed between felt. The precipitate obtained was washed with absolute ethanol and air-dried. The dried polymer was milled, passed through sieve no.60 and stored in a desiccators until further use.

PREFORMULATION STUDIES OF DRUG (DRUG IDENTIFICATION)

MELTING POINT OF SALBUTAMOL SULPHATE

Melting point of salbutamol sulphate was determined by taking a small amount of sample in a capillary tube closed at one end and placed in Thiele's melting point apparatus. The melting point was noted.

UV SPECTRA OF SALBUTAMOL SULPHATE

The UV spectrum ofsalbutamol sulphatewas obtained using Shimadzu UV 1800.Accurately weighed 100 mg of the drug was dissolved in sufficient quantity of distilled water and volume made up to 100 ml known as stock solution (1000 µg/ml). 10 ml of aliquot was withdrawn and volume was made up to 100 ml using distilled water to obtain the concentration of 100 µg/ml. The resultant solution was scanned from 200 to 400 nm and the spectrum was recorded.
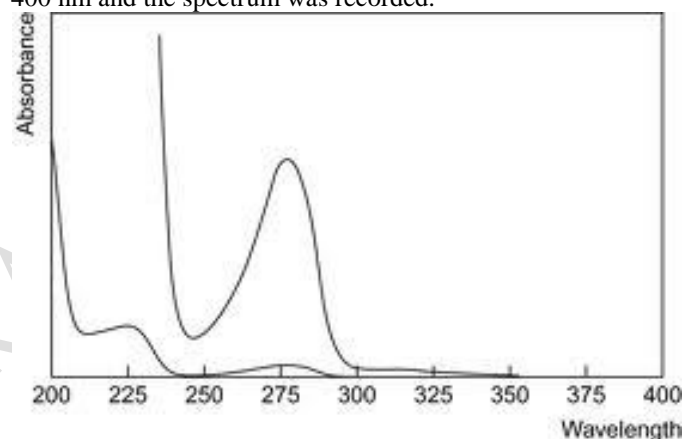

Figure 1: UV spectra of salbutamol sulphate

U.V. SPECTROPHOTOMETRIC METHOD OF ANALYSIS

✓ **STOCK SOLUTION:** An accurately weighed 100 mg of Salbutamol Sulphate was dissolved in 100 ml of distilled water to get solutions of 1000 µg/ml. From this 10ml of solution was withdrawn and diluted upto 100 ml with distilled water to get Salbutamol sulphate stock solution of 100 µg/ml.

✓ **STANDARD SOLUTIONS:** From above stock solutions different aliquot (concentrations) is prepared in the range of 10-100 µg/ml. Solution of Salbutamol sulphate was prepared and scanned and the result showed maxima at 276 nm.

Sr.no.	Concentration (ug/ml)	Absorbance
1	10	0.038
2	20	0.084
3	30	0.124
4	40	0.159
5	50	0.203
6	60	0.245
7	70	0.299
8	80	0.332
9	90	0.379

10	100	0.431

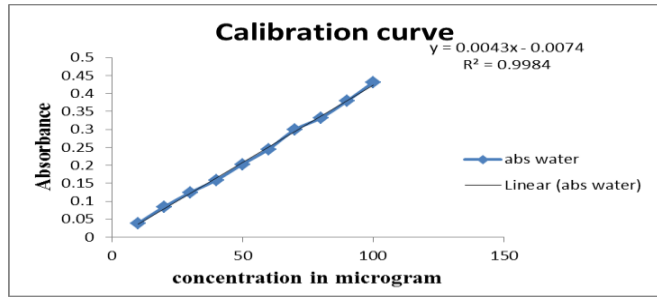*Table 3: Calibration curve of salbutamol sulphate in distilled water*

Figure 2: calibration curve of salbutamol sulphate in distilled water

FTIR COMPATIBILITY STUDIES

✓ FTIR spectra of TSP, salbutamol sulphate and mixture of both

The FTIR spectrum of the isolated polysaccharide is given in Fig.3. It can be used as standard spectrum for quality control and determination of the purity of TSP.
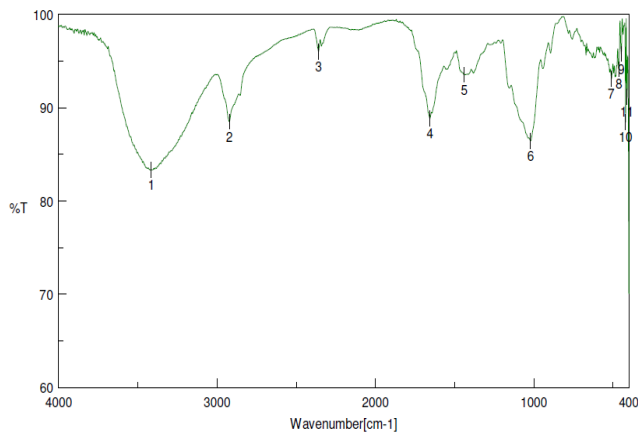

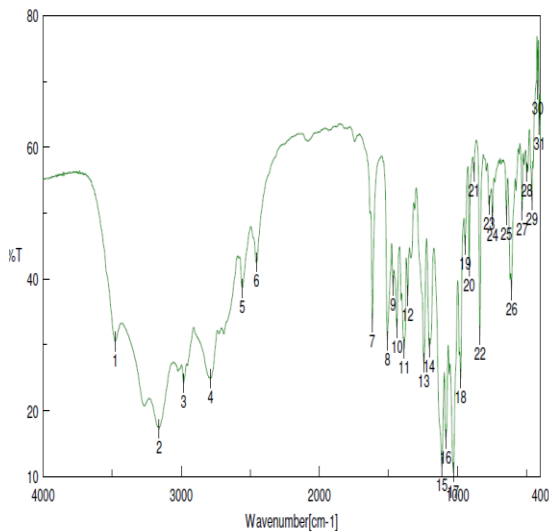*Figure 3: FTIRspectra of TSP (model-Perkin Elmer Spectrum 100)*

Figure 4: FTIR spectra of salbutamol sulphate (model-Perkin Elmer Spectrum 100)
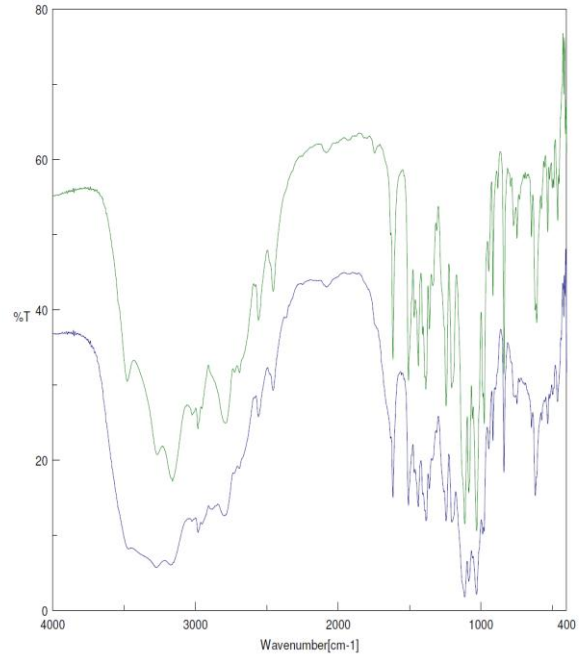

Figure 5: FTIRcompatibility of salbutamol sulphate and TSP (model-Perkin Elmer Spectrum 100)

METHOD OF FORMULATION OF MATRIX TABLETS

Matrix tablets were prepared by direct compression method. The ingredients as given in table were mixed in geometric dilution principle and were blended in a polybag. The blend was compressed using ten station rotatory tablet punching machine (Rimek mini press 1) using 8 mm standard concave punches.

Sr. no	Ingredient	F1	F2	F3	F4	F5	F6
1	Salbutamol sulphate	2 %	2 %	2 %	2 %	2 %	2 %
2	Tamarind seed polysaccharide	10 %	15%	20 %	25 %	30 %	35 %
3	Avicel PH	85 %	80 %	75 %	70 %	65 %	60 %
4	Magnesium Stearate	2 %	2 %	2 %	2 %	2 %	2 %
5	Talc	1 %	1 %	1 %	1 %	1 %	1 %
6	Total percent composition	100 %	100 %	100 %	100 %	100 %	100%
7	Tablet weight	200 mg	200 mg	200mg	200mg	200mg	200 mg

Table 4: Percent Composition of Salbutamol sulphate SR matrix tablet

EVALUATION

EVALUATION OF PRE-COMPRESSIONAL PARAMETER OF TABLET BLENDS

The quality of tablet depends upon the quality of tablets blends from which it is prepared. Therefore, it is quite necessary to evaluate the tablet blends and see whether they

are of required quality or not. All the pre-compressional parameter of tablet blends of each batch like bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose was determined using method and equation given in point number 5.4.9 to 5.4.13of characterization of TSP.

EVALUATION OF PREPARED MATRIX TABLETS

Physical characterization of the matrix tablet (post-compressional parameter)

The properties of the compressed matrix tablets, such as hardness, friability, weight variation, and content uniformity is determined using reported procedure in Indian pharmacopoeia.

✓ *HARDNESS AND FRIABILITY:* The tablet crushing strength, which is the force required to break the tablet by compression in the diametric direction is measured using Monsanto hardness tester for 10 tablets.The friability is determined by testing 20 tablets in Labline friability tester for 4 min at 25 rpm.

✓ *APPEARANCE AND THICKNESS:* The colour, odour and any other flaws like chips, cracks, surface texture, etc. are other important morphological characteristics were observed. The thickne**s**s of the tablets is determined using a Vernier caliper, 20 tablets from each batch were used and average values were calculated.

✓ *WEIGHT VARIATION:* The weight variation is determined by taking weight of 20 tablets using digital electronic balance (Citizen). From each batch twenty tablets were selected at a random and average weight was determined. Then individual tablets were weighed and the individual weight was compared with an average weight, the variation in the weight was expressed in terms of % deviation.

✓ *DRUG CONTENT (CONTENT UNIFORMITY):* The drug content for each batch is determined in triplicate. For each batch 20 tablets are taken, weighed and finely powdered. An accurately weighed quantity of this power is taken and suitably dissolved in water, filtered and analyzed after making appropriate dilutions using U.V. spectrophotometry (Shimadzu 1800).

IN VITRO DISSOLUTION STUDY AND KINETIC MODELINGOF DRUG RELEASE

Release rate of all the formulations are studied up to 12 hours using USP apparatus 2 (Paddle method) at 50 rpm. The Dissolution media is distilled water (900 ml) maintained at 37°C ±0.5°C temperature. Here 900 mldistilled water is used as dissolution medium as the release kinetics of salbutamol sulphate sustained release pellets was found to be independent of the dissolution medium.

Dissolution apparatus	USP Type 2, Paddle
Dissolution media	Distilled water
Volume of the media	900 ml.
Sampling volume	5 ml.
Rotation speed	50 rpm.
Temperature	37 ± 0.5 °C
Regression Equation (Y=m X+c)	Y=0.004x-0.007, R^2=0.998

Table 5: Dissolution parameter

KINETIC MODELING OF DRUG RELEASE

To find out the mechanism of drug release from hydrophilic matrix (TSP), all six formulation of the prepared matrix tablets of salbutamol sulphate are subjected to in vitro release studies. The result obtained in in-vitro release studies are plotted in different kinetic model of release data treatment as follows:

✓ Cumulative percent drug released vs. time (zero order rate kinetics)

✓ Log cumulative percent drug retained vs. time (First Order rate Kinetics)

✓ Log Cumulative percent drug released vs. square root of time (Higuchi's Classical Diffusion Equation)

✓ Log of cumulative % release Vs. log time (Peppas Exponential Equation).

STABILITY STUDIES

An accelerated stability study was conducted for the best batch F5 and F6 for a period of two months in40°C±2°C/75%RH±5%RH. Then the tablets at specific intervals were evaluated for drug content and release study.

DRUG IDENTIFICATION

The sample of salbutamol sulphate procured for study was identified using following parameter-

The average *Melting point* of salbutamol sulphate determined by capillary method was found to be in the range of 156-158 ^{0}C. This is in good agreement with reported melting point.

The *UV spectrum* of salbutamol sulphate solution (100µg/ml) exhibited wavelength of absorbance maximum at 276 nm which complies with the reported.

The UV spectrophotometric method was selected for estimation of salbutamol sulphate. The UV spectrum exhibited maximum absorbance (λ_{max}) at 276 nm. The standard calibration curve exhibited good coefficient of correlation as shown in Table.

Sr.No	Parameters	Observations
1	Absorbance Maximum	276 nm
2	Slope	0.004
3	Intercept	-0.007
4	Correlation Coefficient (r^2)	0.998

Table 6: Standard Calibration Curve Statistics

DRUG EXCIPIENTS COMPATIBILITY STUDY

In physical mixtures (1:1) of salbutamol sulphate and polymer (TSP), there was neither masking of single characteristic peak nor existence of additional peak in drug spectra (Figure.5) so we can conclude that drug and polymers are compatible with each other.

CHARACTERIZATION OF TABLET BLENDS (PRE-COMPRESSIONAL PARAMETER)

The characterization of flow properties of granules is important in tablet compression. The granules with good flow

properties gives uniform die fill and consequently it gives the uniform tablet weight. All fabricated formulations have desirable value for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose and comply with reported specifications mention in table no.13.Indicating required flow property for compression which in turn desirable for content uniformity and less weight variation in final tablets. The experimental result was discussed as below –

Bulk Density And Tapped Density

The bulk density and tapped density of tablet blends of each batch was determined and was found in the range of 0.44 - 0.55 g/ml and 0.48 – 0.62 g/ml respectively indicate good flow.

Carr's Index (Compressibility Index) And Hausner's Ratio

Compressibility index of tablet blend of each batch was determined and was found in the range of 8.33 – 15.09 % indicating the powder blend have the required flow property for compression which is desirable for content uniformity and less weight variation in final tablets. Hausner's ratio of tablet blend of each batch was determined and was found in the range of 1.09 – 1.17 indicating the powder blend has the required flow property for compression.

Angle Of Repose

The angles of repose of tablet blend of each batch was determined and was found in the range of 21.69-26.040 indicate the powder blend have the required flow property for compression.

III. PHYSICAL CHARACTERIZATION OF MATRIX TABLETS (POST-COMPRESSIONAL PARAMETER)

A. APPEARANCE AND THICKNESS

The tablets from all factorial batches were white, circular and concave faced. The surface texture was smooth. The thickness was determined for formulated tablets and tabulated in Table No.15. and found to be in the range of 3.1-3.3 mm for batches F1-F6.

B. HARDNESS TEST

The measured hardness of tablets of each batch ranged between 5.8-6.4 kg/cm^2.This ensures good handling characteristics of all batches.

C. WEIGHT VARIATION

All the formulated tablets passed weight variation test as the % weight variation was within the pharmacopoeial limits of **±7.5%** of the average weight.

D. FRIABILITY TEST

The % friability was less than 1% in all the formulations and ensuring that the tablets were mechanically stable.

E. CONTENT UNIFORMITY

The percentage of drug content for F1 to F6 was found to be between 94.89 and 100.1 % of salbutamol sulphate. it complies with official specifications. The value ensures good uniformity of the drug content in the tablet. Thus all the physical parameters of the compressed matrices were found to be practically within control.

F. IN VITRO DISSOLUTION STUDY AND KINETIC MODELING OF DRUG RELEASE

A plot of cumulative percentage versus time for sustain release matrix tablets revealed that the release pattern was slow. The initial drug release of all formulations were found to be in the range of 19.57-21.31 for the first hour depending on TSP concentration indicate no burst release but the release was fond to be more controlled in later stages in the tablets with higher proportion of TSP. The formulations of TSP having concentration 10%, 15%,20% were failed to sustain release for 12 hours because they indicate 94.50%, 93.82 %, 95.89 % of drug release within 6, 7, 8 hours may be due to burst release of drug respectively. Hence release pattern of formulations no.1,2,3 were not within the desirable limit. However formulations of TSP with concentration 25, 30 and 35 %, the percent release pattern of drug were found be in the range of 97.65 % within 10 hours and 97.89%, 90.59 % within 12 hours. From release pattern study of formulations having concentration 30 and 35 % of TSP, it was found that release rate decreased with increase in TSP proportion and release of drug extended up to 12 hours. The tablets formulations were found to be swell to different extents forming a gel like structures during the release period depending upon the TSP proportion. In order to investigate the release mechanism, the data were fitted to different models representing zero-order, first-order, Higuchi's square root of time V_S Log cumulative percent drug release. From the table no 20, it is concluded that the fabricated tablets followed Higuchi's release for formulation no.1, first order for formulation no.2 and zero order release pattern for formulation no.3 and 4. Further, to understand the drug release mechanism, the data were fitted to peppasmodel that is log time V_S Log cumulative percent drug release. This model is widely used when the release mechanism is not well know or when more than one type oe release phenomenon was involved. The "n" value can be used to characterize release mechanism.

'n'	Mechanism
0.5	Fickian diffusion
0.5<n<1	Non-fickian diffusion
1	Class II transport

The n value for TSP formulations no. five and six ranged from 0.769 and 0.704 Indicating that the release mechanism was non-fickian diffusion.

IV. STABILITY STUDIES

The packed formulations were stored instability chambers maintained at 40°C and 75%relative humidity for one month. From the resultsobtained from the study it was observed that the drug loss on storage was found to be normal result.

The present study was undertaken with an aim to formulate and evaluate the salbutamol sulphate sustain release matrix tablets by using different proportion of TSP. Preformulation study was done initially which include isolation and characterization of TSP, drug identification, FTIR compatibility and result directed for the further course of formulation. Based on preformulation studies different batches of salbutamol sulphate were prepared by using selected excipients. Tablet blends were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose before being compressed as tablets. The tablet blends indicate good flowability which is desirable for content uniformity and less weight variation in final tablets. Various formulations of sustain release matrix tablets of salbutamol sulphate were formulated using different proportion of TSP by direct compression method. The tablets were evaluated for physical characterization, in vitro release study. Observation of all formulations for physical characterization had shown that, all of them comply with the specification of official pharmacopoeias and standard references.Result of in-vitro release profile indicate that among all the formulations, F5 and F6 was found to be better formulations as it showed 97.89 % and 90.59 % drug release within 12 hours. The in-vitro release data was plotted for various kinetic models and indicating zero order for formulations no 5 and 6 with R^2 value 0.983 and 0.952 respectively. The slope of peppas model was found to be 0.769 for F5 and 0.704 for F6 which indicate that drug was released by non-fickian diffusion mechanism. In Stability study it observed that the drug loss on storage was found to be normal.

V. CONCLUSION

The result of the present study demonstrated the isolated natural TSP can be used as a drug release retardant and Drug release was dependent on TSP proportion. The drug release was extended over a period of 12 hours and the mechanism of drug release was observed to be following zero order release. This is mainly due to formation of a thick gel structure that delays drug release from tablet matrix. Thus, the polymer could serve as a new effective drug release retardant exhibited sustained activity of salbutamol sulphate, with better patient compliance. Thus SR matrix tablets of salbutamol sulphate of good quality were prepared by direct compression method and formulation no.5 and 6 considered to be optimized or ideal.

VI. RECOMMENDATION

FUTURE SCOPE

✓ The drug release study profiles can be extended up to 24 hrs

✓ Study can be continued by crosslinkig of TSP with epichlorohydrin to achieve the desired release profile
✓ Study can be continued for in vitro release behavior from TSP alone or by crosslinking by using different suitable concentration of diluents like lactose, dicalsium phosphate and in different P^H conditions.
✓ Study can be continued by using combination of hydrophilic and hydrophobic polymer to achieve the desired release profile.
✓ In vivo studies leading to IVIVC for commercialization.
✓ Study can be continued by using TSP for formulation of drug delivery such as microspheres, microbeads.

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