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Research Article

Preparation and Evaluation of Extended Release Matrix Tablet of Salbutamol Sulphate

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A B S T R A C T

The purpose of this research was to see how the physicochemical properties and porosity of matrix tablets containing various types of natural polymers affected the release of salbutamol sulphate. The sustained drug delivery systems are designed to achieve a constant release of drug from the formulation. The therapeutic levels are adequately maintained throughout the dosing interval. Moreover, the constant rate of absorption also reduces the dosing frequency and thus improves patient compliance. Natural polymer obtained from the gummy exudates and plant fibers. Various natural polymers in use are xanthan gum, acacia, guar gum, agar, carrageenan, chitosan gelatin, etc. With the advancements in technology and insutrial products, natural polymer manufacturing industry has come a long way. India has been serving the polymer producing industry since a long time. Salbutamol sulphate released in a controlled manner to a patient needing this therapy, thereby resulting in a better patient compliance. Accordingly, this study was designed to enhance the bioavailability of drug by prolonging its duration in the stomach as matrix type dosage forms with controlled release. Extended release matrix tablets of salbutamol sulphate were prepared by the direct compression method, using locust bean gum and HPMC K 15M as polymers. The effect of the nature of polymers was studied by preparing various formulations of extended release matrix mucoadhesion tablets.

Keywords: Matrix Tablet, Salbutamol sulphate, Tablet dosage forms, Natural polymers, Extended release dosage forms

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INTRODUCTION:

Oral route has been the most popular and successfully used for controlled delivery of drugs because of convenience and ease of administration. Advances in controlled release technique are attributed for the development of novel biocompatible polymers that allow preparation of novel design dosage forms in a reproducible manner **[1].** Oral administration is also based with inherent physiological constraints such as chemical degradation in stomach, gastric emptying, intestinal motility mucosal surface area, specific absorption sites and metabolic degradation during passage through the mucosa and subsequently the liver with intersubject variability. However, it perhaps difficult to control these factors, subsequently limiting the design of an oral drug delivery **[2].** The matrix system is most often used for a drug controlled release from a pharmaceutical dosage form. Among the innumerable method used in controlled release drug from pharmaceutical dosage form, the matrix system is the most frequently applied; it is release system for delay and control of the release of the drug that is dissolved or dispersed in a resistant supports to disintegration. To define matrix, it is necessary to know the characters that differentiate it from other controlled release dosage forms. Hence the following must be considered **[3-4].** Matrix tablet approach involves the direct compression of blends of drug, retardant material, and additives to form a tablet in which drug is embedded in a matrix core of retardant **[5-6].** Alternative retardant drug blends may be granulated prior to compression. Table 1.1 identifies example of the three classes of retardant materials used to formulate matrix tablets, each class demonstrating a different approach to the matrix concept. The sustained release dosage form is mainly designed for maintaining therapeutic blood or tissue levels of drug for extended period of time with minimized local or systemic adverse effects. This is accomplished by attempting

to obtain Zero order release from the designed dosage form. Zero order release constitutes drug release from the dosage form that is independent of the amount of drug in the delivery system at a constant release rate. Systems that are designed for prolonged release can also be attributed as achieving sustained release delivery systems **[7].** The basic rationale for controlled drug delivery is to alter the pharmacokinetics and pharmacodynamics of therapeutically active moieties by using either po- lymer or modifying parameters inherent in a selected route of administration **[8].** In conventional oral dosage forms, which include capsules, solutions, suspensions and tablets, the drug is released by dissolution or diffusion. The resulting pattern of drug concentration in plasma can vary widely and may cause inconsistent and undesired clinical effects. The high peak blood concentration reached soon after administration may result in adverse effects. With controlled release products the precise rate, extent or timing of drug entry into the blood stream is predetermined or achieved with an integral drug specific composition, structure or mechanism **[9-10].** Pharmaceutical products designed for oral delivery are mainly conventional drug delivery systems, which are designed for immediate release of drug for rapid absorption**.** Salbutamol or albuterol, a moderately selective beta(2)receptor, is widely used as a bronchodilator to manage asthma and other chronic obstructive airway diseases. Salbutamol is readily absorbed from the upper part of gastrointestinal tract, maximum plasma concentration occurs within 2.5 hours & the plasma half life ranges from 2 to 4 hour. In the present study salbutamol sulphate is selected for development of oral sustained drug delivery system (matrix type) on the basis of its pharmaceutical and pharmacoki- netic properties. Salbutamol sulphate is freely soluble in aqueous medium. This drug possesses narrow therapeutic index. Its short half life is 2 to 4 hours. Hence, dosing frequency is high. The present study is aimed to develop and characterize the Guar gum/ Xanthan gum/ and HPMC based Sustained Release Matrix Tablet of Salbutamol and to compare the in vitro dissolution properties of all the formulations. Natural polymers widely used are proteins albumin, globulin, gelatin, collagen, casein, cellulose, chitosan, dextran, algenic acid etc. Biodegradation of polymers occurs in three stages beginning with hydration, loss of strength and mass integrity followed by mass loss. The mechanism of drug release for natural polymers is generally erosion.

MATERIAL AND METHODS

Analytical methods and Estimation of drug: Drug salbutamol sulphate was accurately weighed and dissolved in distilled for determination of absorption maxima (λmax) in solvents i.e. 0.1 N HCl. using UV–VIS scanning spectrophotometer (Shimadzu UV-1800, Japan). The spectrum of these solutions was run in 200 – 400 nm range in double beam UV spectrophotometer (Shimadzu, UV-1800, A11454500755/UV-1800, Shimadzu Corporation, Kyoto, Japan). A spectrophotometric method based on the measurement of absorbance of 2, 4, 6, 8, 10 µg concentration of various aliquates at 258 nm in distilled water was used for estimation of Salbutamol Sulphate.

Preformulation studies: Physicochemical properties of Salbutamol Sulphate were evaluated. Drug excipients compatibility study performed.

Formulation of matrix tablet: The formulation was developed using different polymers. The prepared formulation was studied for its in-vitro release profile, content uniformity and drug assay. The optimized matrix tablets studied for in-vitro dissolution study, mucoadhesive strength, water up-take study and erosion index determination.

- Selection of polymer based on physicochemical property of drug.
- Selection of method for Matrix Tablets

The tablets were prepared by direct compression method. Salbutamol sulphate, locust bean gum and HPMC K15M were sieved through #30 sieves. Magnesium stearate and MCC were sieved through #60 sieves before the use. The amount of drug was kept constant in each formulation (i.e. 100 mg). All the materials were accurately weighed and blended using hand blender and directly compressed on a manual single punch tablet compression machine into 100mg tablets using flat-faced, round punches 8 mm in diameter. The various formulation of 9 batches of the formulation were prepared using locust bean gum and HPMC K15M as polymers, with the ratio of drug to polymer kept as 1:3 **(Table 1).**

Table 1: Various formulations of extended matrix tablets

Formulation code	Drug (mg)	Locust bean gum	HPMC K15M (mg)	Magnesium stearate (mg)	MCC (mg)
SET1	100	35	20	5	15
SET2	100	30	25	5	15
SET3	100	25	30	5	15
SET4	100	25	20	5	15
SET5	100	20	25	5	15
SET6	100	15	30	5	15

Evaluation of granules as Flow properties: Irregular flow of powder from the hopper produces tablets with nonuniform weights. As a result, content uniformity and dose precision cannot be achieved in the production of tablets. Flow properties depend on particle size, shape, porosity and density of the bulk powder, Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane.

$\tan\Theta = h/r$

Where h=height of pile, r = radius of the base of the pile, Θ=angle of repose.

Evaluation parameters for matrix tablet

Weight variation: Not more than two of the individual weights deviate from the average weight by more than the percent shown below and none deviates by more than twice that percent.

Hardness: Hardness of tablet is defined as the force required to break a tablet a in a diametric direction. A tablet was placed between two anvils

Friability: Weigh 10 tablets and place in a friabilator chamber rotated at 25 rpm and they are dropped on distance of 6 inches. The chamber is allowed to rotate for 100 revolutions.

Thickness and diameter: The thickness and diameter of tablets was performed on 20 tablets from each formulation by using Vernier caliper.

Swelling Property: Swelling property was determined by dissolution apparatus. Tablets were introduced in dissolution apparatus containing 900ml of 0.1 N HCL at 50 rpm. The tablets at definite intervals and swollen weight of each tablets was determined by formula.

$$\text{Swelling Index} = \frac{Wt - Wo}{Wo} X100$$

Where-

Wt= weight of tablet at time t

Wo= weight of tablet before immersion

Percent Drug content: 20 tablets from all batches were taken randomly and crushed in pestle-mortar. The weight equivalent to one tablet was taken in volumetric flask (100 ml) and dissolved in 0.1 N HCL and filtered. This solution was analyzed in UV spectrophotometer at λmax 258 nm.

Ex-vivo mucoadhesive strength: The mucoadhesive strength of the tablet formulations was determined by modified physical balance. The assembly consist of a modified double beam physical balance in which left sided pan is removed and attached with glass slide with an additional weight is added with slide to balance the weight of both the pan. Fresh intestine mucosa of goat was used as membrane obtained from local slaughter house and kept in kerb solution during transportation and 0.1 N HCL was use for moistening the mucosa. The underlying mucous membrane was separated by the help of surgical blade and tied with the glass slide with the help of thread. Now the tablet was made to stick with the wooden block and made contact with the mucous membrane and the tablet. The additional weight was increased on the right pan until the tablet detaches from the membrane and the weight used was noted as mucoadhesive strength in grams and force of adhesion was calculated.

***In vitro* Dissolution study:** In vitro dissolution study was carried out using USP type II (basket type) apparatus with 0.1N HCl as a dissolution medium. The temperature was maintained at 37±0.5^{0}C with 50 rotations per minute. 1ml of aliquots were withdrawn at different time intervals and same amount of fresh dissolution medium was replaced to maintain sink condition. The aliquots were analyzed for drug content at λ max 258 nm wavelength using UV-spectrophotometer. The cumulative percentage drug release was calculated and reported.

Results and Discussion: The current research work aimed at developing a novel drug delivery system, in the form of extended release matrix tablet to improve the release of drug for longer period of time to treat the hypertension symptomatically using optimization approach. The absorbance maxima of the salbutamol sulphate pure drug was 258 nm measured by double beam UV spectrophotometer. The organoleptic characteristics of salbutamol sulphate were whitish yellow in color, slightly pungent odor and slightly sweet in taste. The Flow properties of drug were determined in terms of Carr's index (%) 12.38±0.018, Hausner's ratio 1.12±0.014 and Angle of repose θ 26.4±0.121. The solubility of drug at different pH medium was in water 0.00093 mg/ ml and in 0.1 N HCl 0.00156 mg/ ml. The results of physical observation and content determination of both drug sample (S1) and drug with excipients (S2) was observed and was not changes any color, nature etc (Table 2). The FTIR spectra of pure drug and drug with excipients were recorded by FTIR spectrophotometer (IR Affinity, Shimadzu, Japan) and result was concluded that there was no interaction between both material as due to presence of same wavelength in both FTIR spectra (Figure 2 - 3). The peaks were determined and observed peaks were compared with standard. Extended release matrix tablets of salbutamol sulphate were prepared by the direct compression method, using locust bean gum and HPMC K 15M as polymers for mucoadhesive agent. The effect of the nature of polymers was studied by preparing various formulations of extended release matrix tablets. In all these formulations, a constant amount of drug (100 mg) was maintained. The blend was initially characterized for pre-compression and post- compression parameters. Pre-compression characterization was done for angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio. The results of pre-compression characterization includes angle of repose (21.65-26.77°), bulk density (0299-0.385 g/cm^3), tapped density (0.417 - 0.473 g/cm^3), Carr's index (14-25 - 36.78 %) and Hausners ratio was found to be (1.16 – 1.58). Post-compression characterization includes thickness, hardness, friability, weight variation, drug content and in-vitro drug release. %. The average weights of the entire prepared tablet were 97.15±.05mg to 103.27±.01mg which was within the specified limit. The thickness of all the tablets was in the range of 2.59 to 2.51 um. The hardness of all the formulated tablets was found to be in the range of 4-7kg/cm^2. Friability was found to be 0.31 to 0.91. The swelling Index for all tablets was found in the range of 66.25±0.21 to 70.08±0.37. The bioadhesive strength was found to be in the range of 11.03 to 23.12. The results of the present research work indicated the successful formulation of matrix tablet with excellent ex-vivo bioadhesive properties and drug release profile. The drug content of the entire prepared tablet was found to be 95.29±0.98 to 102.32±2.16. The drug content of tablets complied with the limit as 85-110% as per IP specifications (IP 2007) (Table 3). From the in vitro drug

release studies, it was found that in formulations SET4 showed best sustained release profile. Among the nine formulations (SET1 to SET6) prepared formulations SET4 was found to be the best formulations in terms of sustained drug release. Drug release kinetics was performed by using various kinetic models such as Zero order, First order, Korsmeyer- Peppas and Higuchi's equation.

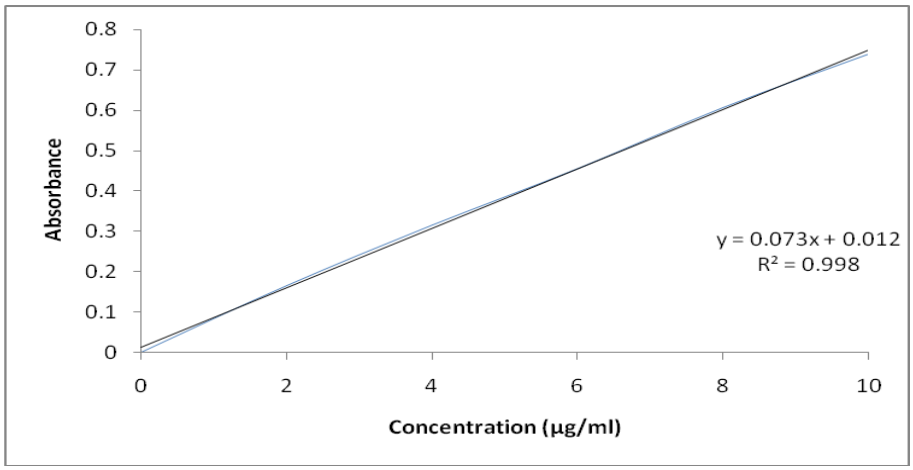

Figure 1: Calibration curve of drug Salbutamol Sulphate in 0.1 NHcl

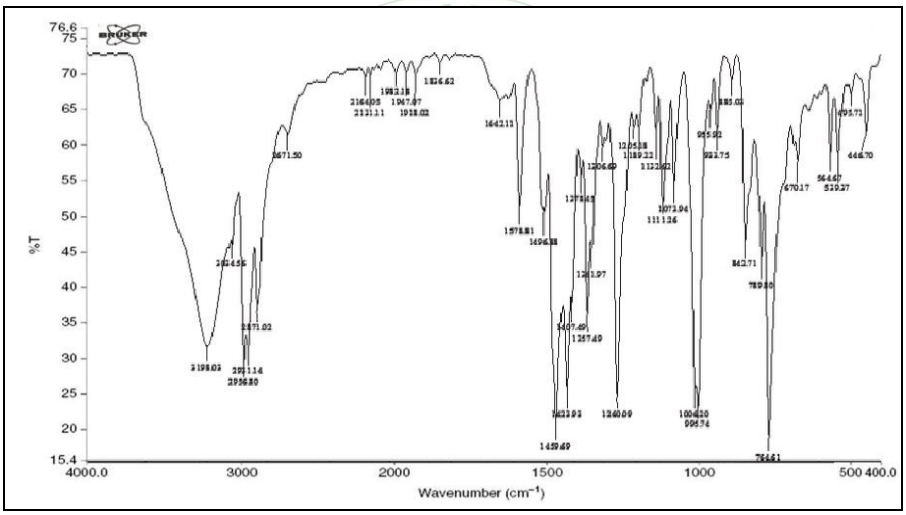

Figure 2: The I. R. Spectrum of sample of pure drug (S1)

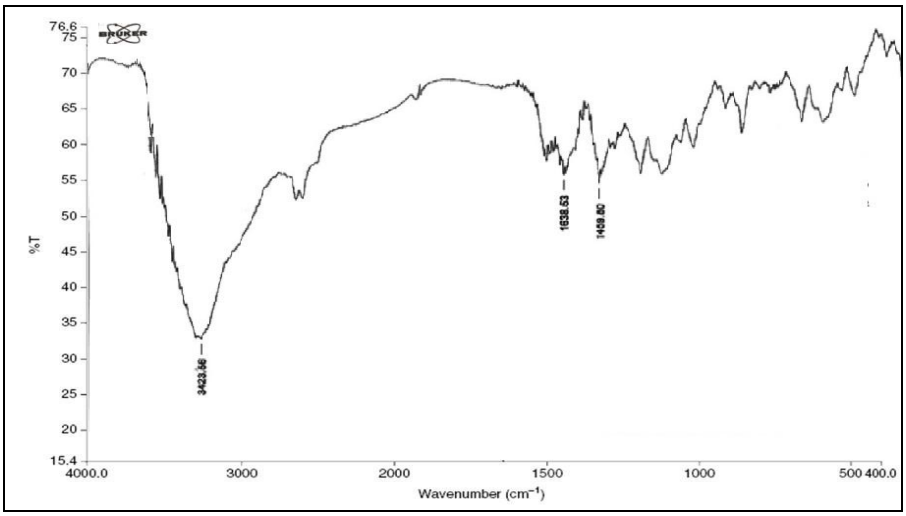

Figure 3: The I. R. Spectrum of sample of drug and all excipients (S2)

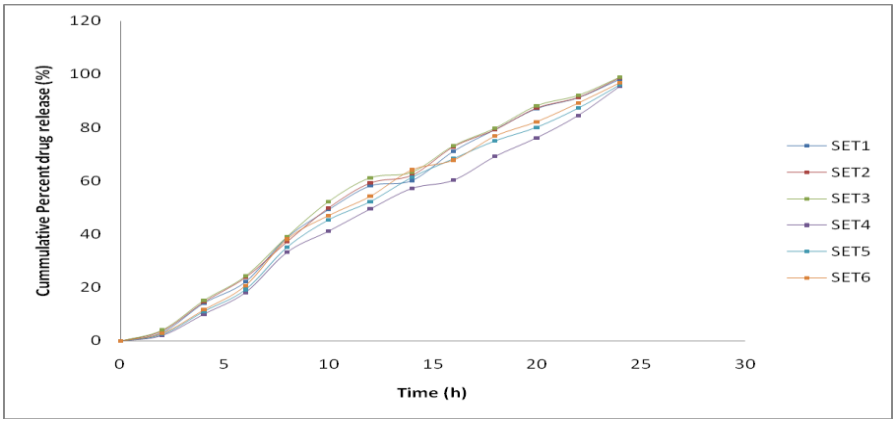

Figure 4: Zero-order release of various batches (SET1-SET6)

Table 2: Pre-compression characterization

Formulation code	Bulk density (g/cm^3)	Tapped density (g/cm^3)	Carr's index (%)	Hausner's Ratio	Angle of Repose (Θ)
SET1	0.358	0.433	17.32	1.21	26.77
SET2	0.365	0.464	21.33	1.27	22.33
SET3	0.385	0.449	14.25	1.16	26.18
SET4	0.343	0.437	21.51	1.27	24.88
SET5	0.369	0.465	20.64	1.26	21.65
SET6	0.278	0.421	33.81	1.51	27.64

Table 3: Post compression characterization

F. code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Hardness (kg/cm^2)	Friability (%)	Swelling Index	Mucoadhesive strength (gm)	Drug content (%)
SET1	190.59±0.04	2.54±0.09	8.1±0.02	5.74±0.78	0.91±0.89	70.08±0.37	23.12±0.1	97.52±0.26
SET2	190.07±0.01	2.51±0.04	8.2±0.01	5.54±0.42	0.41±0.46	69.05±0.08	21.02±0.5	97.08±0.08
SET3	191.28±0.04	2.59±0.01	8.1±0.02	5.51±0.91	0.46±0.43	66.87±0.19	20.17±0.2	95.29±0.98
SET4	193.27±0.01	2.53±0.01	8.1±0.02	7.04±0.41	0.31±0.67	68.88±0.25	19.36±0.4	97.15±0.45
SET5	191.73±0.03	2.59±0.01	8.1±0.01	6.31±0.27	0.52±0.43	67.62±0.03	18.56±0.2	95.65±1.14
SET6	194.24±0.06	2.56±0.02	8.1±0.01	6.30±0.28	0.65±0.23	66.71±0.31	14.52±0.1	96.91±0.82

Summary and Conclusion: The proposed work was under the investigation of an extended release matrix tablet of salbutamol sulphate for antihypertensive therapy. The formulation was able to drug released from controlled-release oral preparations in the stomach region for absorbed, specifically in the gastrointestinal tract, leads to bioavailability problems. The formulations of Salbutamol Sulphate based on designed to enhance the bioavailability by prolonging its duration in the stomach via the controlled release

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