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Research Article

FORMULATION AND EVALUATION OF NOVEL SUSTAINED RELESE CAPSULES OF TERBUTALINE SULPHATE

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ABSTRACT
Terbutaline sulphate is a direct acting sympathomimetic agent with predominantly β- adrenergic activity and a selective action on β_2-receptors, which is widely used in the prophylaxis and control of asthma. In the present investigation, the empty gelatin capsules (body) were cross linked by exposing to the vapours of formaldehyde in order to extend the drug release. The drug was filled in to the cross linked capsules by using hand filling method. Macroscopical features revealed that drug was dispersed in the polymer matrix. The empty capsules were subjected for various physicochemical tests like appearance, dimension, identification, weight and moisture content. The prepared capsules were evaluated for their thickness, content uniformity, weight variation, disintegration and *in-vitro* dissolution. The average weight and thickness of all the capsules were uniform. *In-vitro* dissolution studies showed a burst release initially followed by a progressive fall and a constant release of the drug and extended up to 8 to 10 hours. Release kinetics of terbutaline sulphte from cross linked capsules followed the first order release profile.

KEYWORDS: Sustained release, Capsules, Crosslinking, Terbutaline Sulphate, Asthma.

INTRODUCTION

During the last two decades there has been a remarkable increase interest in sustained release of drug delivery systems[1]. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and improvement in the therapeutic efficacy and safety achieved by these delivery systems [2].

Sustained release, sustained action, prolonged action, controlled release, extended action, timed release etc., are terms used to identify drug delivery systems that are designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of single dose[3]. Sustained drug delivery systems are able to provide very precise control over drug release for a prolonged period of time eliminating the need for frequent dosing and minimizing side effects, thereby increasing patient compliance and comfort[4].

Asthma is a predisposition to chronic inflammation of the lungs in which the airways (bronchi) are reversibly narrowed. Asthma affects a total of 350 million peoples across the world. As the people grow older this will found to rise[5].

Terbutaline sulphate is an effective broncho dilator and relatively short acting $ß_2$ – adrenergic agonist. It has shorter biological half life of 3-4 hours and it is effective at a low oral dose of 5mg. Terbutaline sulphhate produces many of its pharmacological effects by activation of adenyl cyclase, the enzyme which catalyses the conversion of adenosine triphosphte to cyclic adenosine monophosphte. Terebutaline is incompletely absorbed from the GIT and also subject to extensive first pass metabolism by sulphate conjugation in the liver and possibly by the gut wall. It is used in the treatment of Asthma,

chronic bronchitis, emphysema and other bronchopulmonary disorders involving bronchospasm, in doses which do not produce marked cardiac acceleration[6].

Incorporation of drugs in polymeric matrices is a widely used approach for prolonging the drug release. Matrix devices have many advantages over the other controlled release devices as they cannot undergo sudden dose dumping. Matrix devices gives a higher initial release rate and can be made to release the drug at a nearly constant rate. As the terbutaline sulphate having shorter biological half life and low oral dose, an attempt was made to develop sustained release drug delivery system containing terbutaline sulphate for controlling the conditions like nocturnal Asthma[7].

MATERIALS AND METHODS

Terbutaline Sulphate a gift sample from Astra Zeneca, Bangalore, Sodium carboxy methyl cellulose, hydroxyl ethyl cellulose, hydroxyl propyl methyl cellulose were obtained from Loba Chemicals Pvt. Ltd., Mumbai. Sodium Alginate from Degussa India Pvt. Ltd., Mumbai. All other chemicals used in this study were of analytical grade.

Preparation of Crosslinked Gelatin Capsules

Hard gelatin capsules about 200 in number of size-2 were taken and their body was separated from the cap, then body was placed on a wire mesh. 25ml of 37% v/v of formaldehyde solution was taken in a 100ml beaker and kept in an empty desiccator and 2.5 gms of potassium permanganate was added to this. On the top of the beaker the wire mesh containing the body of the capsule was kept and immediately closed with a filter paper tied around its mouth[8].

The body of the capsule was made to react with formaldehyde vapours for 4 hours. Then they were removed and kept on a filter paper in a hot air oven at 45^{o}C for 48 hours so that there is a complete reaction between formaldehyde and gelatin will take place. Then capsules were kept in an open atmosphere for a week to make sure that the residual formaldehyde gets evaporated. Then these capsule bodies were capped with caps (not exposed to formaldehyde) and were stored in a polythene bag[8].

Evaluation Tests for empty gelatin capsules

Various physical and chemical tests were carried out simultaneously for both formaldehyde treated and untreated capsules.

Physical Tests

Identification attributes

The 10 capsules each of formalin treated and untreated were randomly selected, and then checked their lockablity, odour and sticky[9].

Visual defects

The 10 capsules each of formalin treated and untreated were randomly selected, and then checked for change in colour and shape manually[9].

Size/dimensions

The 10 capsules each of formalin treated and untreated were randomly selected, and determined their length, external diameter and thickness using screw gauge[9].

Weight

The 10 capsules each of formalin treated and untreated were randomly selected, and determined their weight by using single pan electronic balance and calculated the average weight of capsules[9].

Moisture content

About 1 gm of sample capsules was weighed accurately and kept in an oven for drying at 100-125 for 17 hours, then capsules were cooled an a descicator and reweighed. The moisture content was calculated on the basis of loss on drying, which is expressed in terms of percentages[8].

Solubility

The empty gelatin capsules (both formaldehyde treated and untreated) were stirred in a beaker containing 100ml of dissolution medium by using magnetic stirrer. The dissolution medium taken was water, buffers (pH 1.2 and 7.2). The time at which capsule dissolves or forms soft fluffy mass was noted[8].

Chemical Tests

This test is a modification of the limit test for formaldehyde (method A, IP 1996) carried out for absorbed tetatnus, pertusis and diphtheria vaccine[10].

Standard formaldehyde solution

Diluted a suitable volume of formaldehyde solution with water to obtain a concentration of 0.002%w/v.

Sample solution

Formalin treated body of the capsules were cut into small pieces and transferred to a beaker containing distilled water. This was mixed with a magnetic stirrer for one hour to solubilize free formaldehyde. Then it was filtered into 50 ml volumetric flask, washed with distilled water and the volume was made up with the washings.

Procedure

Added 9 ml of water to 1ml of sample of solution. Taken 1ml of this solution and added 4ml of water and 5ml of acetyl acetone reagent, warmed this mixture on water bath for 40^{o}C then allowed to stand for 40 min. Similarly standard solution was also prepared by using standard formaldehyde solution and compared the intensity of colour developed was compared.

Formulation of Sustained Release Drug Delivery System

Preparation of physical mixture of drug and polymer

Accurately weighed polymer was geometrically diluted with weighed amount of lactose using mortar and pestle. Added the weighed amount of terbutaline sulphate to the above mixture and thoroughly mixed then stored in polythene bag[8].

The various formulations by using different polymers and the ratios of polymers: diluent: drug are given in table-1.

Filling of capsules

Hard gelatin capsules of size 2 with formalin treated body and untreated cap were taken for filling. 20 capsules for each formulation were prepared by manual method as follows.

The cap and body of the known weight of capsule was separated individually by hand. The quantity of physical mixture equivalent to 7.5mg of drug (terbutaline sulphate) was filled in to the body of capsule. The remaining volume of the capsule body was filled with lactose and pressed tightly with the help of glass plunger. Finally the cap was locked into the capsule body and stored in tightly packed container for further studies.[8]

Evaluation of Drug Loaded Capsules

Compatibility studies were conducted using IR spectroscopy and TLC of drug alone, and with polymer. Various physico-chemical properties such as content uniformity, weight variation, disintegration, dissolution and stability studies were determined on prepared capsules.

Individual weights of 20 capsules were determined by using an electronic single pan balance. The percentage moisture loss was determined by keeping the weighed capsules in a desiccator containing anhydrous calcium chloride. After 3 days, the capsules were taken out and re-weighed; the percentage moisture loss was calculated using formula (initial weight-final weight/ initial weight) x 100 [9].

Content uniformity

The contents of the capsule was emptied into 100ml volumetric flask containing 50ml distilled water and shaken well until the drug was completely dissolved. The solution was filtered and the volume was made up to the mark quantitatively with distilled water to get stock solution A.

1.0 ml of p-nitroaniline solution (0.2% w/v in 10% v/v Hcl) was added to 25ml volumetric flask followed by 1.0 ml of sodium nitrite (0.5% w/v in water). The two solutions were mixed well and allowed to stand at room temperature for 10 minutes.

1.0 ml of methanol was next added and mixed well to eliminate the excess of nitrous acid that was formed insitu, followed by the addition of 1ml of stock solution A.

2.0 ml of sodium hydroxide solution (6%w/v in water) was added into the above flask. The orange colour was formed within 2 minutes. Make up the volume to 25ml with distilled water. The absorbance of the resulting solution was measured at 450 nm using UV-Visible spectrophotometer and a concentration was estimated[10].

Disintegration Test

6 capsules were placed in each of the six tubes of the basket. Perforated plastic discs were then placed on the top of the capsules and the buffer (pH 1.2) was used as dissolution media. Then the disintegration apparatus was operated and test was carried out for all the formulations[9].

***In-Vitro* dissolution Studies**

The dissolution studies were carried out by rotating basket method as specified in USP by using Electro lab, tablet dissolution tester. One capsule was taken and placed in the basket, and it was immersed into the dissolution medium (37^{o}C ± 0.5^{o}C) carefully by avoiding air bubbles and the basket was rotated at 100rpm.

The dissolution was first carried out in 500 ml of pH 1.2 buffer for 2 hours and in 500 ml of pH 7.2 buffer for the remaining period of 10 hours. At each intervals of 1 hour, 10 ml of the dissolution media was withdrawn and same volume was replaced by dissolution media. The amount of drug dissoluted in withdrawn media can be estimated as earlier[10].

Stability Studies

The selected formulations were packed in an air tight polythene bag and stored at 60^{o}C and 45^{o}C for a period of 3 and 10 weeks respectively. The samples were withdrawn at the end of 5th ,8th and 10th week in case formulations stored at 45^{o}C and 1st , 2nd and 3rd week in case formulations stored at 60^{o}C. All the samples were evaluated for any physical change, drug content, disintegration time and *In vitro* dissolution test.

RESULTS

Formalin treatment has been employed to modify the solubility of gelatin capsules. Exposure to formalin vapours or treatment with aqueous formalin results in an unpredictable decrease in solubility of gelatin owing to cross-linkage of the gelatin molecule initiated by the aldehyde.

All the empty capsules were lockable type, odourless, soft and sticky when touched with wet finger. After formalin treatment, there were no significant changes in the capsules except for the stickiness. The body of the capsules was hard and non sticking even when touched with wet finger.

The physico- chemical evaluation data of empty gelatin capsules presented in table 2 indicates that the thickness of the capsule ranges from 0.15 – 0.19 mm. The capsules with formalin treated showed higher thickness compared to untreated. The individual weights of each capsules are quite uniform and cross-linking did not show any significant change in weight. The length of the cap was 10.85mm where as body was 18.12 and 18.25mm for formalin treated and untreated respectively. The external diameter was found to 6.74 and 6.81 for formalin treated and untreated respectively.

Average weight of capsules was in the range of 97.22 to 98.42 mg. The percentage moisture was 12.69 for formalin treated and 15.73 for untreated, this may be due to cross linking that leads to decrease in percentage moisture.

The solubility studies on both formalin treated and untreated capsule shells was carried out for 24 hrs. The study shows in case of untreated capsules both body and cap were dissolves within 15 minutes, where as in formalin treated capsules only cap dissolves within 15 minutes and the body remained intact.

The qualitative test performed for free formaldehyde showed that the sample solution was not more intensely coloured than the standard solution, inferring that less than 20µg of free formaldehyde is present in 25 capsule bodies. Hence it is considered as a valid container for the drug dispersed in hydrophilic polymer matrix intended for sustained release preparation.

The amount of physical mixture was found to be 97.4 to 97.6 mg as per the combination of polymers, diluent and drug in 3:9:1 ratio. The amount of terbutaline sulphate ie dose of a drug in each capsule was 7.44 - 7.56 mg and percentage drug content was from 99.2 – 100.8, the data is shown in table-3.

The disintegration test showed that the cap of the capsules were disintegrated within 15 minutes, while the body of the capsules were remain unchanged even after 60 minutes.

From the *In vitro* dissolution studies it was found that all the caps were separated from the body within 15 minutes. The dissolution profiles of all the formulations from figure-1, showed a higher initial release rate, which is a characteristic property of the matrix formulations. The data of the *In vitro* dissolution for the different time intervals was given in table-4. The drug release followed first order kinetics and their release rate constants were found to be 0.0833,0.0919, 0.095 and 0.04 hr^{-1} for SRC-I, SRC-2,SRC-3 and SRC-4 respectively.

The stability studies showed no change in the physical changes and appearance. The data given in table 5 indicates that there is no significant changes in content estimation, disintegration time and dissolution profile.

DISCUSSION

The present work is an attempt to develop sustained release capsules of terbutaline sulphate on the lines of novel drug delivery systems. This system is capable of releasing its contents at predetermined time. The system consists of water soluble cap and insoluble body of the capsule. The drug is placed in the body of capsule, sealed and plugged with a hydrogel plug. Then the cap is fixed to the body of the capsule. On oral ingestion of the dosage form, the cap dissolves in the gastric medium and the hydrogel plug swells. The swollen plug is ejected from the body of the capsule releasing the drug at a predetermined rate.

The results of the excipient compatibility studies revealed that there is no chemical interaction between the drug and excipients and the drug is maintained in its original state.

The first step in preparing such type of drug delivery system is to prepare capsules with soluble cap and insoluble body. It was done by exposing the separated body of capsule to formaldehyde vapours, which causes a crosslinkage of the gelatin molecule making it insoluble.

The next objective of preparing the sustained release capsules of terbutaline sulphate was achieved by filling the physical mixture of the drug and the hydrophilic polymer into the above capsules. The physical mixture was made by mixing the drug with diluents and different polymers.

The formulations were subjected for various physicochemical tests, disintegration and dissolution studies. The percentage of drug content in all the formulations was found to be within the range of 99.06 to 100.8 and the cap was disintegrated within 15 minutes.

In vitro dissolution profile revealed that in all the formulations the cap was dissolved within 15 minutes, and then there was a higher initial release of drug followed by a slow and a nearly constant release of drug over a period of 8 to 10 hours depending on the type and amount of polymer used. The drug release followed first order kinetics, indicated that the release rate dependent on the amount of drug remaining in the dosage form.

From the accelerated stability data it was observed that there was no significant changes in the physical properties of the capsules, drug content, disintegration time and the dissolution studies, hence the formulations are quite stable.

Finally to conclude just mixing of the drug with a blend of polymers and filling the mixture into cross linked gelatin capsules prolongs the release of drug. When the two doses of drug were placed between the two polymer plugs within the crosslinked capsules showed sustained release behavior.

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Table 1: Composition of different formulations

Sl.No	Formulation Code	Ratio of the for Polymer:Diluent:Drug (3:9:1)		
		Polymer 3	Diluent 9	Drug 1
1	SRC-1	Sodium carboxy methyl cellulose	lactose	Terbutaline Sulphate
2	SRC-2	Hydroxy ethyl cellulose	lactose	Terbutaline Sulphate
3	SRC-3	Sodium alginate	lactose	Terbutaline Sulphate
4	SRC-4	Hydroxy Propyl Methyl Cellulose	lactose	Terbutaline Sulphate

Table 2: Physical characteristics of empty gelatin capsules with and without cross-linking*.

Type of Capsules	Length (mm)		External diameter (mm)		Thickness (mm)		Length of Capsules (mm)		Avg Weight (mg)	Percent moisture
	Cap	Body	Cap	body	Cap	body	Before Locking	After Locking		
Formalin Treated	--	18.12	--	6.74	--	0.19			97.22	12.69
Untreated	10.85	18.25	7.64	6.81	0.18	0.15			98.42	15.73

*Each value is a mean and standard deviation of six determinations.

Table 3: Amount of Physical mixture and drug loading per capsule

Formulation Code	Amount of Physical mixture filled (mg)	Amount of drug per capsule (mg)	Percentage drug content
SRC-1	97.4 ± 1.2	7.56 ± 2.3	100.8 ± 2.5
SRC-2	97.5 ± 1.3	7.48 ± 1.5	99.73 ± 2.6
SRC-3	97.4 ± 2.1	7.53 ± 1.7	100.4 ± 2.4
SRC-4	97.6 ± 1.9	7.44 ± 1.1	99.20 ± 2.1

Table 4: *In-Vitro* dissolution profile of various formulations

Time (hrs)	Cumulative Percentage drug released ±SD			
	SRC-1	SRC-2	SRC-3	SRC-4
1	39.14 ± 3.2	38.76 ± 3.0	37.82 ± 2.5	17.00 ± 3.2
2	47.04 ± 1.1	45.05 ± 2.5	45.00 ± 1.6	24.00 ± 1.7
3	61.00 ± 2.2	56.52 ± 2.7	56.42 ± 3.4	26.00 ± 2.0
4	68.48 ± 2.9	61.42 ± 2.1	66.00 ± 3.1	35.00 ± 1.1
5	93.41 ± 3.0	71.56 ± 1.9	89.00 ± 1.1	44.00 ± 1.8
6	99.90 ± 2.1	82.61 ± 2.0	96.00 ± 2.4	59.00 ± 1.3
7		84.02 ± 1.6		71.00 ± 2.1
8		94.80 ± 1.2		91.00 ± 2.4
9		98.36 ± 3.1		95.00 ± 2.1
10				96.00 ± 3.0

*Each value is a mean and standard deviation of six determinations.

Table 5: Stability data of all the formulations

Formulations	Stability tests	Storage Temp 60°C			Storage Temp 45°C		
		1week	2week	3week	5week	8week	10week
SRC-1	Drug Content	7.51	7.48	7.44	7.49	7.46	7.42
	Disintegration Time (min)	14.52	13.60	14.22	15.36	15.25	14.34
SRC-2	Drug Content	7.36	7.42	7.45	7.40	7.38	7.41
	Disintegration Time (min)	13.42	15.26	14.24	13.55	14.42	14.29
SRC-3	Drug Content	7.35	7.31	7.28	7.37	7.35	7.32
	Disintegration Time (min)	14.23	15.46	13.44	15.55	13.42	15.29
SRC-4	Drug Content	7.48	7.45	7.39	7.49	7.46	7.41
	Disintegration Time (min)	15.23	13.26	13.48	15.46	14.32	13.39

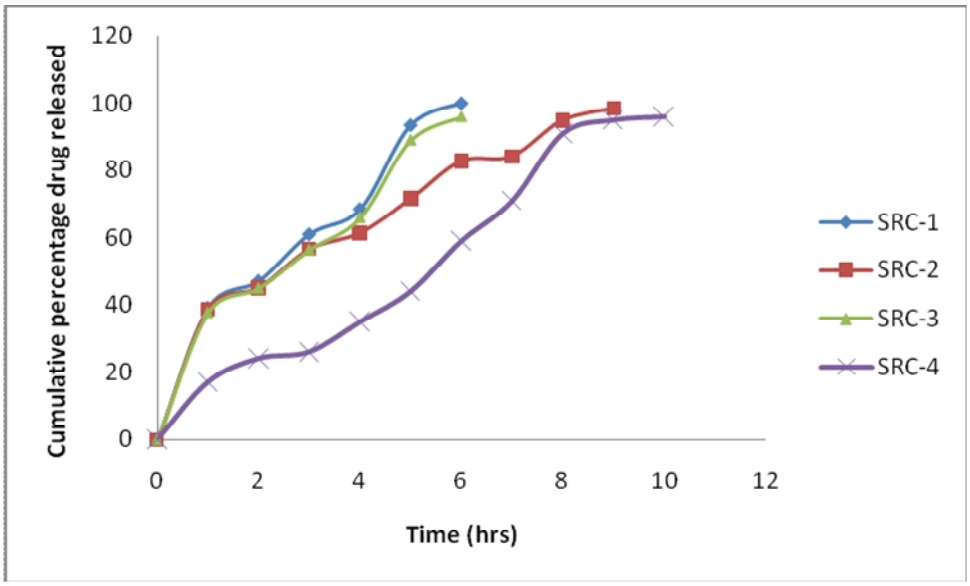

Figure 1: *In vitro* dissolution profile of various formulations

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