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DEVELOPMENT AND CHARACTERIZATION OF CHRONOMODULATED DRUG DELIVERY SYSTEM OF SALBUTAMOL SULPHATE

Kanika Arora*, Suman Jain and Manoj Sharma

School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior

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Corresponding Author:

Kanika Arora

*School of Studies in Pharmaceutical Sciences, Jiwaji University, Gwalior

E-mail:
kanika_littleangel@yahoo.co.in

ABSTRACT

Pulsatile drug delivery system is the most interesting time and site specific system. This system is designed for chronopharmacotherapy which is based on the circardian rhythm. The present study is aiming at the development of Chronotherapy designed according to the chronological behavior of body. Although oral delivery has become a widely accepted route of administration of therapeutic drugs, the gastrointestinal tract presents several formidable barriers to drug delivery. In this study our aim was to develop and evaluate an oral pulsatile drug delivery system of salbutamol in capsule device. Cores containing salbutamol as model drug were prepared by granulation of different disintigrants Croscarmellose sodium and microcrystalline cellulose. Then the treatment of gelatin capsule bodies with formaldehyde and filling the granules into the capsule bodies. The coating material Eudragit RL 100 was used in different concentration. The five formulations of different concentrations were prepared by using drug and polymer. Coating material used in coating of capsule body. Finally the prepared formulation was evaluated for all evaluation parameters like hardness, dissolution, disintegration and other parameters. Salbutamol release from pulsatile capsule was studied. Dissolution showed that the enteric coat of the Eudragit RL100 was intact for 2 hrs in pH 1.2 but dissolved in intestinal pH and also dissolved in pH 7.4, thus leaving the soluble cap of capsule. Exposed polymer plug absorbed the surrounding fluid got swelled and drug was release.

Keywords: Pulsatile drug delivery system, salbutamol, chronotherapy, circardian rhythm, Eudragit RL100, Croscarmellose.

INTRODUCTION

Pulsatile drug delivery system is defined as the rapid and transient release of certain amount of drug molecules within a short time period immediately after a predetermined off-release period, i.e. lag time .Pulsatile drug delivery aim to release drug on programmed pattern at appropriate time and at appropriate site of action. Pulsatile system is gaining a lot of interest as it is increasing patient compliance by providing time and site-specific drug delivery.[1,2,3] In these systems, there is rapid and transient release of a contain amount of drug molecule within a short time-period immediately after a predetermined off release period. Various techniques are available for the Pulsatile delivery like pH dependent systems, time dependent system, micro-flora activated system etc. which can be designed as per the physiology of disease and properties of the drug molecules.[4,5] It is the one type of drug delivery system, where the delivery device is capable of releasing drug after predetermined time delay known as Pulsatile drug delivery system. Salbutamol sulphate is a short-acting, relatively selective β2-adrenergic bronchodilator used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease. [6] A pharmaceutical dosage form is the means by which drug delivered to specific sites of a body**.** These are obtained from two specific sources- Synthetic sources and natural sources. Formulation of drug in pure form is usually difficult. Pharmaceutical dosage form may be solid form, semisolid form, and liquid form. The dosage forms are a sophisticated drug delivery system. They provide mechanism for safe delivery of accurate dosage.[7] pulsatile delivery is desirable for drugs acting locally or having an absorption window in the gastro-intestinal tract or for drugs with an extensive first pass metabolism, e.g. h-blockers or for drugs, which develop biological tolerance, where the constant presence of the drug at the site of action diminishes the therapeutic effect, or for drugs with special pharmacokinetic features designed according to the circadian rhythm of human[8-11]. Most Pulsatile drug delivery systems are reservoir devices covered with a barrier coating. The barrier can dissolve, erode or rupture during/after a certain lag time, after which the drug is released rapidly from the inner reservoir core. The rupturing of the barriers are induced by an expanding core upon water penetration through the barrier coating.[12-18]

Important of this Pharmaceutical Dosage Form

- Protect the drug substance from the atmospheric oxygen or humidity.
- Protect the drug substance from the destructive influence of gastric acid after oral administration.
- Inhibit the bitter taste of drug, salty or offensive or odor of a drug substance.
- Provide liquid preparation of substances that is either insoluble or unstable in the desired vehicle.
- Provide liquid dosage form of substances.
- Provide rate controlled drug release.
- Provide optimal drug from topical administration.
- Provide for insertion of a drug into one of the body orifices.
- Provide site of drug directly in the bloodstream of body.
- Provide for optimal action of drug through inhalation therapy.

SALBUTAMOL

Salbutamol is a short-acting β2-adrenergic receptor agonist used for the relief of brochopasma in condition such as asthma and chronic obstructive pulmonary disease[19]. Salbutamol was the first selective β2-receptor agonist to be marketed in 1968. It was first sold by ALLEN & HANBURYS (UK) under the brand name ventolin, and has been used for the treatment of asthma and COPD. The drug was an instant success, and has been used for the treatment of asthma ever since. Salbutamol sulfate is usually given by the inhaled route for direct on bronchial smooth muscle. Salbutamol is rapidly absorbed after oral administration and undergoes presystemic metabolism in the gut, oral bioavailability is 50%.

Pharmacokinetic Data

- Oral bioavailability: 50%
- Metabolism: it is subject to first pass metabolism in the liver
- Half life : 4 hours
- Excretion: readily excreted in the urine as metabolic and unchanged drug some execrate in faces.
- Protein binding :14-25%
- Predicted water solubility: sparingly soluble in water, soluble in ethanol (96%), slightly soluble in ether.
- Synthesis**:** salbutamol can be prepared from an acetophenone derivative which is itself derived from salicylic acid.

Medical Use

- Salbutamol is typically used to treat brochopasma as well as chronic obstructive pulmonary disease.
- Salbutamol has been used in treating acute hyperkalemia on account of its potassium depleting properties by stimulating in flow in cells.

Mechanism of Action

Salbutamol stimulates β2 adrenergic receptors which are predominant receptor in bronchial smooth muscle. This increase of cyclic AMP relaxes bronchial smooth muscle and decrease airway resistance by lowering intracellular ionic calcium concentration. Salbutamol relaxes the smooth muscles of airway, from trachea to terminal bronchioles. Increased cyclic AMP concentration is also inhibits the release of bronchoconstrictor mediator such as histamine, leukoterne from the mast cell in the airway.

MATERIALS AND METHOD

Salbutamol was obtained as gift sample from Jigchem Universal, Mumbai India. Eudragit RL-100, Evonik industries obtained from East West College of pharmacy Bangalore. Cellulose Acetate Phthalate was received from Central drug house pvt. Ltd New Delhi. Polyvinyl pyrrolidone was received from Himedia laboratories Pvt.Ltd, Talc was received from central drug laboratories house, SLS was received from Himedia laboratories pvt. Ltd.

Preformulation Studies of Drug

Analysis of Drug

Salbutamol was identified by ultraviolet spectroscopy.

Ultra violet Spectral Analysis:

The unsaturation of drug couled with the presence of the Chromospheres will influence the extent of absorption and whether UV or visible light will absorb. The UV spectrum of drug in solution is very suitable for quantitative e analytical work and serve as conditional information for the structural validation of compound in drug identification studies.

Analysis of Absorbance of Salbutamol by UV Spectrophotometer:

Determine the λmax of salbutamol, standard stock solution of salbutamol in distilled water was prepared. Then find the absorbance in between 200-400 nm by using UV spectrophotometer .The peak was found at 242nm.

FTIR Spectral Analysis:

FTIR is the studied of interaction of infrared light with matter. FTIR is sensitive to the presence of chemical functional groups in a simple. The powerful aspect of FTIR is that it identification of unknown functional groups of drug. The wave number positions of the band of a functional group are known. This information used to identify that functional group in the drug sample. Another use of infrared spectra is in confirming identities which involves comparing the spectra of two samples to each other for determining whether the

samples have the same composition or not. The peak intensity in infrared spectrum is proportional to concentration and they can be used to measure concentration.

Infrared spectroscopy spectrum of salbutamol was obtained by means of a FTIR spectrophotometer. The samples were prepared and measurements were attempted with accumulation of 15 scans and a resolution of 5 cm^{-1} over the range of 400-4000cm^{-1}. After the running spectrum relating to major fundamental group were identified. A spectrum of the subsequent sample of the same compound was compared with original spectra. FTIR studies of salbutamol physical mixture of drug with polymers were carried out to find out the interaction and absorbance.

Analysis Oof Partition Co-efficient of Salbutamol

When a substance is added to immiscible solvents in an amount insufficient to saturate the two phases, it gets distributed in a definite concentration ratio. In general, a definite lipid partition of drug is a prerequisite for the absorption of a drug to take place from a specific site. Unionized drug generally have high lipid solubility and the drug, which are unionized but have a high dipole moments have low lipid solubility.

The partition coefficient is the ratio of unionized drug distributed between the organic and aqueous phase at equilibrium. For a drug delivery system, lipophilic and hydrophilic balance has shown to be a contributing factor for rate and extent of drug absorption. The measurement of drug lipophilicity and its ability to cross the lipoidal cell membrane is determined by oil and water partition coefficient in system such as water/octanol and octanol and water /buffer.

The partition coefficient of salbutamol was determined in solvent system n-octanol and distilled water and phosphate buffers. Weighed accurate quantity of drug was taken in a stoppered glass tube containing 5ml of n-octanol. After dissolving the drug in n-octanol, 5ml distilled water was added it test tube and in another tube octanol and saline phosphate buffer was taken. Then the glass tube was set to equilibrate by shaking in mechanical shaker for 6 hrs and after shaking, the tube was transferred into separating funnel kept overnight 37±2ºC for equilibrium. The content and both were separated. After appropriate dilution the aqueous phase was analyzed for salbutamol against reagent blank solution using ultra violet spectrophotometer. The drug concentration in n-octanol phase was determined by the amount in aqueous phase from the total content of drug added to the tube.

Analysis of Solubility of Salbutamol

1gm salbutamol was taken in a test tube. 1ml of solvent was added to it. It was shaken for some time. If clear solution seen, drug was considered to be partially soluble. If clear solution not seen 9ml more solvent added if solution obtained drug was considered to be soluble. This process was continued till clear solution was not obtained.

Melting Point Analysis

Melting point of salbutamol was determined by using capillary tube method. In this method the sample was taken in small capillary tube which was closed on one side and then set the tetrameter and then metal block was heated and temperature was noted when it started to melting.

METHOD

Preparation of Salbutamol Granules

Firstly all the ingredients were mixed and then moistened with 10% poly villain solution in Ethanol. There mixture was granulated by passing through a 22-mesh screen. Then dried at 120ºC - 140ºC. The mixture was sized through 42 mesh screen talc was added and mixed.

Table 1: Formula of Granules

Ingredient	Quantity per capsule	Quantity for 20 capsule
Salbutamol	25 mg	500 mg
Lactose	100mg	2300 mg
Microcrystalline cellulose	25mg	500 mg
Talc	10 mg	200 mg
Magnesium stearate	25mg	500 mg
PVP	15mg	300mg

Table 2: Composition of Formulation

FC	Weight of drug granules (mg)	Polymer used	Weight of polymer (mg)
F1	200mg	Eudragit RL 100	15
F2	200mg	Eudragit RL 100	25
F3	200mg	Eudragit RL 100	35
F4	200mg	Eudragit RL 100	45
F5	200mg	Eudragit RL 100	55

Evaluation of Designed Pulsatile Capsule

The capsules were selected and weighed individual for weight variation. The test requirement are met is none of the individual weight are less than 90% or more than 110% of the average.

Table 3: Weight of capsule before and after coating

S. NO.	Weight Before Coating	Weight After Coating	Weight Gained
1.	237.37	243.25	5.88
2.	235.24	241.65	6.41
3.	237.12	246.73	9.61
4.	237.13	245.34	8.21
5.	237.00	246.16	9.16

Result & Discussions

Identification of Drug

U. V Spectrophotometric analysis Studies

UV scanning spectra of drug was given in-(figure 1)
This gave absorption λmax at 242nm.

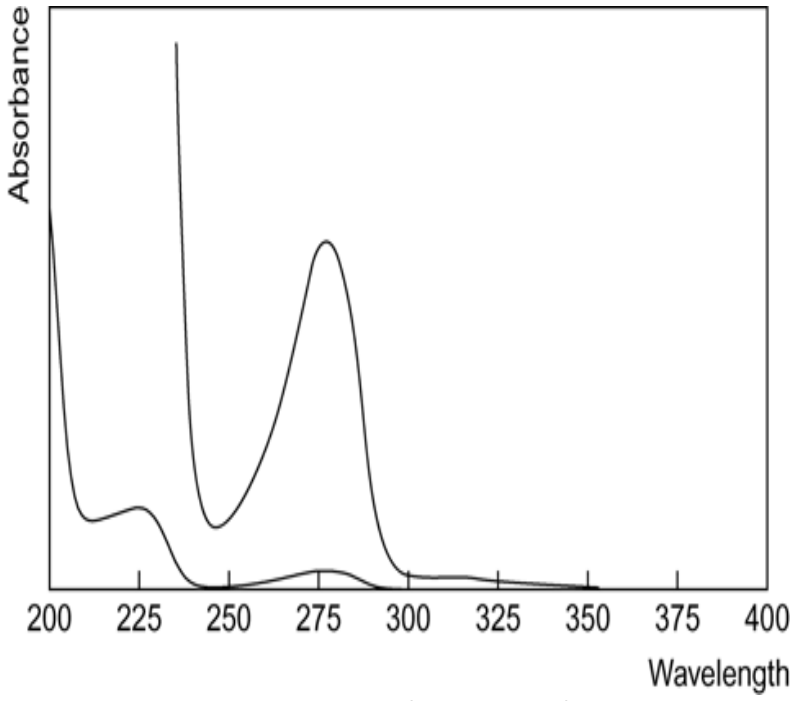

Figure 1: UV spectrophotometric studies

Partition Coefficient Analysis:

Partition coefficient of salbutamol was determined out in distilled water and n-octanol and n-octanol and phosphate buffer result are 0.412 and 0.522 which shows drug is hydrophilic in nature.

Table 4: Solubility of salbutamol in various solvents

	Partition coefficients value	
Salbutamol	Water/n-octanol	n-octanol/phosphate buffer
	0.412	0.522

Melting point analysis

The melting point of salbutamol was determined they are melted at 156ºC.

Table 5: Melting point of salbutamol

Drug	Melting point
Salbutamol	156ºC

Solubility Analysis Study:

Solubility of salbutamol was carried out in various solvents-

- water
- methanol
- ethanol
- chloroform

Table 6: Salbutamol solubility in various solvents

S. NO.	Solvents	Solubility
1.	Water	Sparingly soluble
2.	Ether	Slightly soluble
3.	Ethanol	Soluble
4.	Chloroform	Very soluble

Preparation of Standard Curve of Salbutamol in Various Solvents:

Standard Curve of Salbutamol in Distilled Water

Standard curve of salbutamol in distilled water was determined by firstly Stock solution of salbutamol 1000µg/ml was prepared by dissolving accurately quantity of salbutamol in distilled water by shaking and solution of appropriate concentration was made by dilution of stock solution with distilled water. The calibration curve standard contained of salbutamol. The absorbance of each dilution of solution was noted at 242nm. Calibration curve were plotting absorbance versus concentration of drug expressed in µg/ml.

Table 7: Concentration of drug was expressed

S.NO.	Concentration	Absorbance
0	0	0
1.	1	0.020
2.	2	0.043
3.	3	0.062
4.	4	0.085
5.	5	0.102
6.	6	0.122
7.	7	0.143
8.	8	0.165
9.	9	0.189
10.	10	0.211

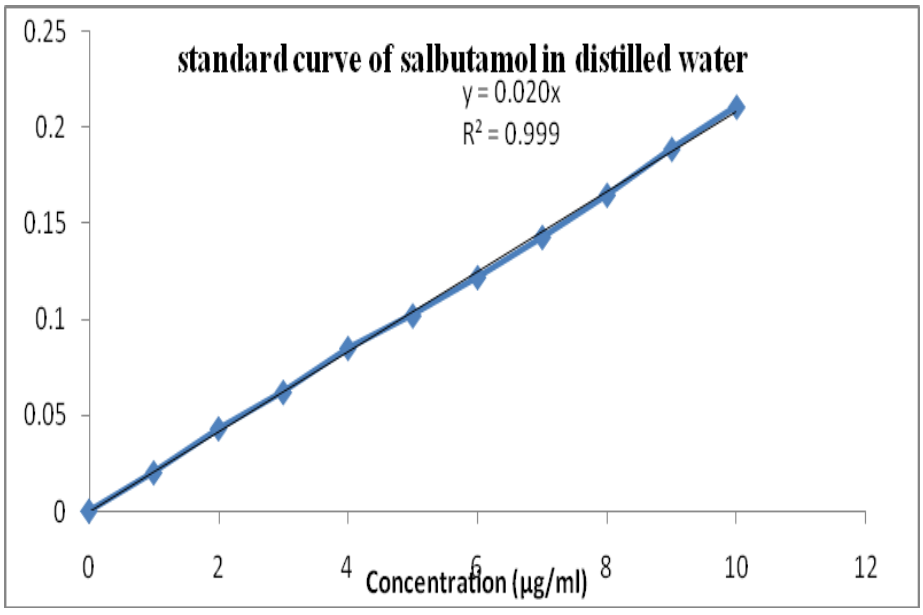

Figure 2: Standard curve of salbutamol in distilled water

Standard Curve of Salbutamol in Phosphate Buffer Ph 7.4

Standard curve of salbutamol in phosphate buffer Ph 7.4 were determined firstly taken 10 mg drug of salbutamol was weighed and dissolved by shaking and volume was made up to the mark with phosphate buffer so the resulting solution contained 1000µg/ml salbutamol as stock solution. then preparation of dilution firstly taken 1 ml of this solution was transferred into 100ml volumetric flask and volume was made up with phosphate buffer from this solution the aliquots were taken and volume was made up to 10 ml with phosphate buffer saline to prepare the dilution containing 1µg/ml - 10µ/ml of drug. These solutions were analyzed.

Table 8: Standard curve of salbutamol in phosphate buffer pH 7.4

S. NO.	Concentration	Absorbance
0.	0	0
1.	1	0.098
2.	2	0.009
3.	3	0.153
4.	4	0.204
5.	5	0.255
6.	6	0.308
7.	7	0.358
8.	8	0.414
9.	9	0.471
10.	10	0.528

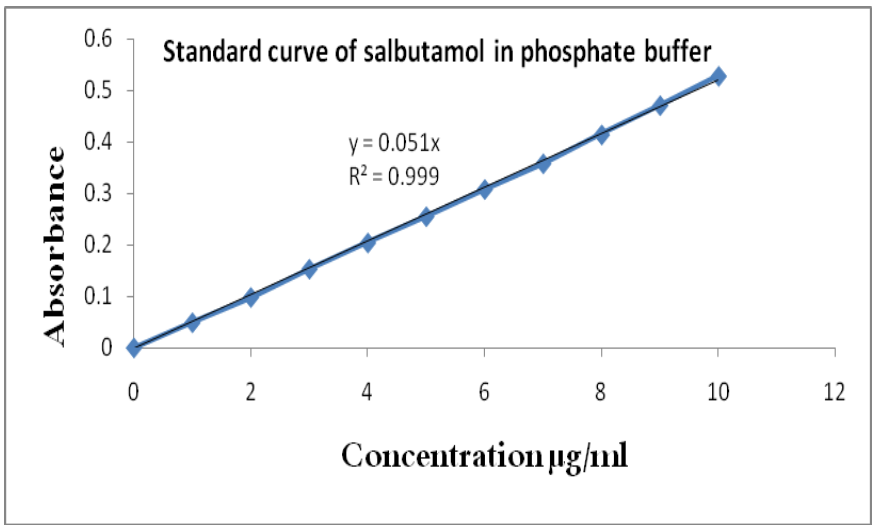

Figure 3: Standard curve of salbutamol in phosphate buffer

Micromeritic Properties of Granules of Salbutamol

Bulk density and Tapped density : (Table 9)

Angle of Repose: (Table 9)

Table 9: Micromeritic properties of granules of salbutamol

Granules code	Bulk Density	Tapped Density	Angle of Repose
	Mean	Mean	Mean
1	0.3	0.52	22.35
2	0.42	0.61	21.10
3	0.44	0.48	20.15

Hausner's ratio:
Hausner's ratio is an indirect index of ease of powder flow. upon considering the Micromeritic properties of all formulation, formulation 3 of granules had best flow properties.

Carr's index:
Carr's index from 5.76-9.13%. Formulation 3 of granules had lowest Carr's index indicating excellent compressibility.

Table 10: Carr's Index & Hausner's ratio of Prepared Granules

Granules code	Hausner's ratio	Particle size	Carr's index
	Mean	Mean	Mean
1	1.02	0.718	6.06
2	1.08	0.607	9.20
3	1.04	0.662	5.80

Formaldehyde Treatment of Capsules

Formaldehyde treatment has been employed to modify the solubility of the capsules. Formaldehyde vapors resulted in an unpredictable decrease in solubility of gelatin to the cross linkage of the amino groups in the gelatin molecular chain with aldehydes group of formaldehyde. Capsule bodies treated with formaldehyde, out of them about ten were found to be distorted. Capsule of 250mg capacity showed decrease in length and diameter after treatment. The solubility tests were carried out for normal capsule and formaldehyde treated capsules for 24hr.

Table 11: Dissolution Study Formaldehyde treated Capsules

S. NO.	Dissolution time of cap (in mins)	Dissolution time of capsules body (in hrs)
1.	18	24
2.	19	24
3.	21	24
4.	20	24
5	17	24
6.	19	24
7.	20	24
8.	22	24
9	19	24
10.	18	24

Evaluation of Pulsatile Capsule of Salbutamol:

Salbutamol release from Pulsatile capsule was studied. Dissolution showed that the enteric coat of the Eudragit RL 100was intact for 2 hrs in pH 1.2 but dissolved in intestinal pH and also dissolved in pH 7.4, thus leaving the soluble cap of capsule. Exposed polymer plug absorbed the surrounding fluid got swelled and drug

release. After wetting of the plug it is formed a soft mass which was then ejected out of the capsule body and released the drug. With all the formulation there was absolutely no drug release in pH 1.2

Determination of Time of Erosion of Plugs

The time for complete erosion of the plug was determined with a disintegration tester in pH 7.4 phosphate buffer solution.

In Vitro Dissolution Analysis

In-vitro dissolution studies were carried out on the Pulsatile at 37±0.5ºC at 100rpm using USP dissolution apparatus-II. The in-vitro dissolution studies were performed in three different pH media in order to the changes along the GI tract. Capsules were tied to paddle with a thread, in dissolution media consisting of 900ml of 0.1 N hydrochloric acid and dissolution was performed for 2 hrs. Then removed that first media and the fresh pH 6.8 phosphate buffer solution was added. After 3 hrs then the medium was removed and fresh pH 7.4 dissolution medium was added for subsequent hrs. 1 ml of sample was withdrawn at each hrs and replaced with the same volume of test medium is dilute withdrawn sample if required and then estimated for salbutamol concentration at 242nm. Finally the drug content in all fluids were determined from calibration curve of salbutamol determine the release pattern.

Table 12: Comparative release study of formulation

Time (hrs)	Formulation Code				
	F1	F2	F3	F4	F5
	Mean	Mean	Mean	Mean	Mean
0	00.00	00.00	00.00	00.00	00.00
1	00.00	00.00	00.00	00.00	00.00
2	00.00	00.00	00.00	00.00	00.00
3	00.00	00.00	00.00	00.00	00.00
4	00.00	00.00	00.00	00.00	00.00
5	09.60	04.20	00.00	00.00	00.00
6	45.20	48.10	14.12	0.41	00.00
7	96.20	89.50	44.60	17.60	09.38
8	98.20	92.00	91.10	81.00	71.60
9	98.40	96.20	93.30	90.30	87.20

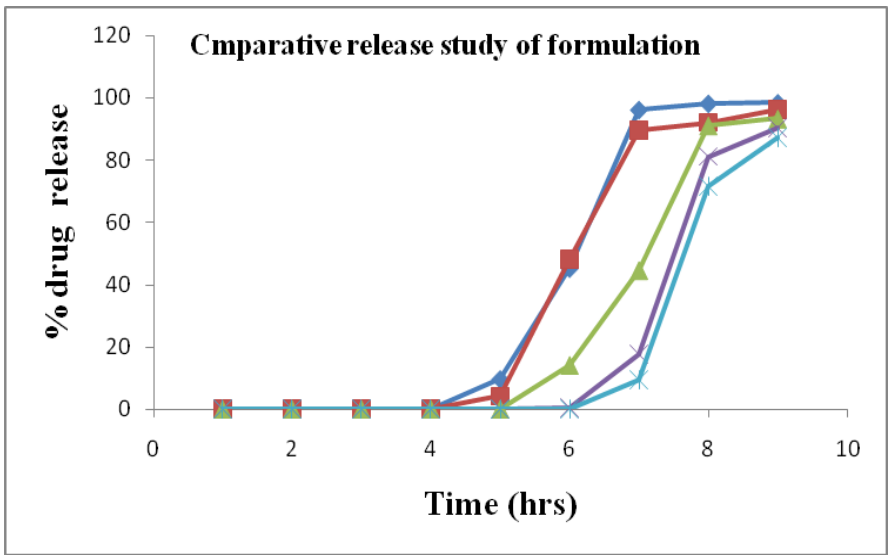

Figure 4: Comparative Release Study Of Formulation

CONCLUSION

Salbutamol granules were filled into capsule bodies and at open end of capsule bodes hydrogel plug were inserted then cap were fitted. A hydrogel plug seals the drug contain into capsules body. When this capsule body came into contact with dissolution media the hydrogel plug swelled and after lag time the plug pushed and rapidly releases the drug.

The study was to design Pulsatile release capsule of salbutamol. The release of the drug after a lad time consistent with requirement was achieved with developed formulation. The hydrogel plug Eudragit was found to be responsible for release. These capsules may be helpful for patient.

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