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Research Article

Formulation and Evaluation of Pulsatile drug delivery of Albuterol sulphate and Theophylline drugs using modified Pulsincap technology

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Abstract

Albuterol Sulphate and Theophylline are used as anti-asthma agents. The objective of the present investigation was to design develop and evaluate a modified pulsincap drug delivery system of Albuterol Sulphate and Theophylline for the treatment of Asthma. The body of capsule was made insoluble with water by cross linking with formaldehyde. This modified capsule was completely filled with drug with polymer such as HPMCK15M, HPMC K 100M, PVPK-30 to expel the drug after predetermined lag time. A hydrogel plug was inserted in the body of a capsule to obtain desired drug release after a lag time for chronotherapy of asthma. Untreated capsule was attached to the treated body and was released. The drug was exerted to precompression parameter such as Angle of repose, Bulk density, Tapped density, Car's index Hassner's ratio. These capsules were subjected to further post formulation studies such as weight variation, drug content, invitro dissolution studies separately. The pre and post formulation parameters were found to be within permissible limit. The mere compatibility of drug, polymer and excipients were determined by Fourier transform infrared analysis (FTIR) and UV-Visible spectroscopy (UV). The results showed that drug was completely compatible with polymer and excipients. In vitro dissolution were carried out by using pH 6 .8 and pH 7.4 buffers. Based on the result obtained F5 Formulation shows good dissolution profile. Higuchi, Hixson crowell. Koresmeyer peppas to evaluate the kinetics and drug release. The drug release follows first order kinetics and the mechanism was found to be NON FICKS DIFFUSION.

Keywords: Albuterol Sulphate, Theophylline, modified pulsincap drug delivery system, FTIR, Dissolution

INTRODUCTION

The chronomodulated pulsatile drug delivery system is framed suitable to the body's chircardian rhythm. The main objective and function of PDDS is rationalized for sustained release of drug at that particular site.[1]. There exist many situations where the drug fails to promote efficient with sustained release formulations. Hence to overcome ,there requires the drug release after a lag time. Usually the body follows the circadian rhythm in all the functions of the body with increased or decreased activity with respect to time. Examples may be like hormones like cortisol, aldosterone have their periodical fluctuations at the blood vessels or levels. For the severity of diseases like bronchial asthma, myocardial infraction, Rheumatoid arthritis and hypertension is time dependent. The delivery system where the desired delivery is released after 6-8 hours after the time of administration (during early hours) is ideal case for PDDS. Modified pulsincap is a single unit capsular PDDS. It holds and consists of a capsular body which is insoluble along with soluble cap and hydrogel plug [2]. Here the plug is eroded later after predetermine lag time by erosion, when comes in contact with GI fluid the plug swells and push outside from capsule, The idea/design is based on retarding the time of release of drug till the system travels from oral cavity to colon [3]. The present study orients to develop pulsatile capsule of albuterol sulphate which are single unit system follows the lagtime which is totally controlled by the hydrogel plug polymers. The important constituent of capsule is gelatin and to delay the hydrolysis of capsule formaldehyde is utilized..Here the body of capsule was made hardened by vapour of formaldehyde to prevent capsule body dissolution .The main objective of the present work was to formulate a nano unit pulsatile capsules of albuterol sulphate which releases the drug after a predefined lag time and gives required concentration of drug at periodical intervals of time.

RESEARCH METHODOLOGY

Materials: Theophylline and Albuterol Sulphate of analytical grade were procured from Yarrow chem. products, Mumbai. HPMC K 100M, HPMCK15M and other polymers and excipients were purchased from S D fine-chem limited, Mumbai,

Drug –Characterization UV Spectroscopy

Calibration curve of albuterol sulphate was plotted with water, pH 1.2, 7.4 and 6.8 buffer with different concentration (1, 2, 3, 4, 5 µg/ml). The absorbance of the solution was taken at wavelength 225 nm against the blank solution. (UV

spectroscopy 400-200 nm, Shimadzu, Japan 1601) [4].

Fourier Transform Infrared (FT-IR) Spectroscopy[4]

Infrared spectroscopy was used to predict possible drug excipients interaction using a FTIR spectrometer (8400S, Shimadzu, Japan) at 4000-400cm $^{-1}$.

Differential Scanning Calorimetry (DSC)

Thermogram of drug was carried out by using DSC. In this study approximately 5 mg of sample were taken and heated 0^0C to 450 ^{0}C at heating rate 10°C/min. Thermo gram obtained by using DSC (METLLER DSC 1 STAR SYSTEM, Zürich, Switzerland) [4].

Preparation of Hydrogel plug:

Hydroxy propyl methyl cellulose (HPMC k_{100}M), spray dried Lactose were mixed for 10minutes. Magnesium stearate (1%) was added to the previous mixture and further blended for 5 minutes and compressed using single punch tablet machine.[5]

Physico-Chemical Characterization of Hydrogel Plug:

Shape and appearance

Hydrogel plug s were examined under a lens for the shape of the tablet, colour was observed by keeping the tablets in light.

Weight Uniformity

Ten tablets were weighed individually on electric balance from which the mean was calculated, and the percentage deviations were determined.

Thickness

The thicknesses often tablets were determined using a Vernier calliper and the mean of these readings was taken as the mean of the tablet thickness.

Friability

The friability of the tablets was determined using the Roche friabilator. Five tablets were weighed and put into the friabilator and set to rotate at 25 rounds per minute for about four minutes. The tablets were then removed and weighed again. The friability (F) is given by the formula;

Preparation of theophylline and albuterol sulfate pellets

Pellets containing theophylline and albuterol sulfate were created using the extrusion-spheronization pelletization process. For 15 minutes, the following ingredients were ground: theophylline and albuterol sulfate, lactose, aerosil, and crosscarmellose sodium. After passing through Sieve No. 40, pelletization followed in a planetary mixer, the afore mentioned medication and excipient mixture were thoroughly blended for 15 minutes. To create a dough mass that was then extruded using a piston extruder,the PVPK-30-isopropyl mixture was employed as a binder solution and slowly added to the aforementioned blend for 30 minutes (1 mm orifice).In the fourth step, the theophylline extrudates were spheronized for 10 minutes at 750 rpm (air velocity: 1 kg/cm2). In a fluidized bed dryer, these pellets were dried for 24 hours .[6]

Preparation of core tablets

The direct compression method was adopted where the ingredients were passed to sieve number 30, and put through sieve number 40 to break up any lumps. In a double cone blender, the medication, cross-carmellose sodium, CCS (Ac- di-sol), L-HPC (LH 11), Avicel PH 112, and Lactose anhydrous (with or without) were combined to create the blends for the core tablets. Step by step, purified talc and magnesium stearate were added and further combined.

Preparation of Cross-Linked Gelatine Capsules

Formalin treatment has been employed to modify the solubility of gelatine capsules. Exposure to formalin vapours results in an unpredictable decrease in solubility of gelatine owing to the cross- linkage of the amino group in the gelatine molecular chain aldehyde group of formaldehyde by Schiff's base condensation.[7]

Physicochemical characterization of formaldehyde treated empty gelatin capsules

Length of the capsule, external diameter of the capsule, thickness of the capsule was determined.

Qualitative test for free formaldehyde

Standard used is formaldehyde solution and sample solution is formaldehyde treated bodies (about 25 capsules), cut into small pieces and taken into a beaker containing distilled water. This was stirred for 1 hrs with a magnetic stirrer, to solubilize the free formaldehyde. The solution was then filtered into a 50 ml volumetric flask, washed with distilled water and volume was made up to 50 ml with the washings.[8].

Solubility study of treated capsules [9,10].

The capsule bodies were exposed to 15% formaldehyde solution in varying time intervals. Then exposed capsule bodies were dried in hot air oven. The solubility of bodies was tested in 0.1N HCL. The time at which the capsule dissolves or forms a soft fluffy mass was noted.

Results and Discussion

The study was undertaken to prepare pulsatile release capsules using chronomodulated drug delivery. The study was planned to characterize the prepared pulsatile capsules for various parameters. The observations were recorded as follows:

Drug –Characterization UV Spectroscopy

Determination of maximum wavelength was carried out to find out maximum absorption of each compound. This was because maximum absorption could be used for qualitative analysis of a compound where the value of λ_{max} was specific for each compound. Theophylline absorption spectrum. It shows the maximum absorption of theophylline with 0.1 N NaOH solvent was obtained at a wavelength of 277 nm, and the measured solution concentration was 10 ppm with an absorbance of 0.538 A. The findings demonstrate that the calibration curve follows Beer Lambert law and is linear in the range of 2 to 18 g/ml.

Fourier Transform Infrared (FT-IR) Spectroscopy

To identify theophylline and albuterol sulphate, they were determined for qualitative analysis using infrared absorption spectroscopy. The IR spectrum of the pure drug shown many functional groups with characteristic peaks like carboxylic acid at 1714.93 cm-1, C=C, CH2 at 1445.79 cm-1, amide c=o at 1669.23 cm-1, C=C, C=N, NH at 1565.39 cm-1,and OH at 3431.64 cm-1.

Differential Scanning Calorimetry (DSC)

Through simultaneous differential scanning calorimeter, thermal curves of each sample of pure drug, physical mixture of drug with individual excipients such as croscarmellose sodium, aerosil, lactose, and PVPK-30, and for albuterol sulphate HPMC K 100M, HPMC K 15M, Sodium

Bicarbonate, Lactose monohydrate NF powder, Microcrystalline cellulose, Magnesium Stearate, and Talc were recorded (DSC). Pure medicine DSC thermogram Theophylline showed a single, abrupt melting endothermic peak at 273.2°C and 206.6°C, which is consistent with the drug's melting points of 272°C and 201°C, respectively, which also suggests that theophylline is crystalline and anhydrous.

Preparation of Hydrogel plug:

The composition of optimal formulation was determined as weight of push tablet 138 mg (coded value: +0.59), plug tablet 60 mg (coded value: +0.49) and coating weight gain of 8.4 mg (coded value: -0.82). The results showed that the optimal formulation of PRCs had lag time of 4.5 h and release at 6 h and 12 h are 61.95% and 96.29% respectively.

Solubility study of treated capsules.

Then the solubility tests were performed with distilled water,7.4 phosphate buffers and pH 1.2, 6.8 buffers and other medias for 24 and 48 hours . It was noticed that pH 7.4 exhibits the best solubility of around 99.93 0.30 & 98.89 0.29 during a 48-hour period, whereas distilled water exhibits the least solubility of 79.99 1.21 of theophylline and albuterol sulphate solubility,

Preparation of theophylline and albuterol sulfate pellets

A random sample of 20 micro pellets was taken and sizes were determined by using vernier caliper in triplicate. The size of the prepared pellets was found to be in the range of 1.54 ± 0.13 to 1.86 ± 0.15 mm in diameter. As the concentration of sodium alginate increases, size of beads increases because of less shrinkage in higher concentration beads. Similarly, size of beads increases with addition of talc may be because of less shrinkage after drying. The surface of the beads was found to be spherical and smooth in nature. The surface of the beads was found to be spherical and smooth in nature except for B1 (2% sodium alginate), B4 (2% CaCl2) and B6 (30 minute cross linking time). The ionotropic gelation method was used to prepare Alginate beads of DRUG and optimized beads were coated with mixture of eudragit polymers. There was no interaction found between the drug and the excipients. There was no significant difference in release profile observed between Ca++ & Zn++ cross linked beads. Whereas, slight slow release was observed in case of chitosan reinforced beads.

Preparation of Cross-Linked Gelatine pellets

The cross linked beads were coated with an outer rupturable layer of polymer blend eudragit RSPO/RLPO in different ratio (80:20, 70:30, 60:40) at different weight gain (8-12% w/w). A 2-factor 3-level, face centered CCD was designed to execute the experiments. Eudragit RLPO made up 23.33 percent of the ideal formulation's coating composition (coded value: -0.66), while coating weight gain made up 9.84 percent (coded value: - 0.08). The findings indicated that the optimal release and had a lag time of (4.5 h) and a 74.9 percent release at 6 h.

CONCLUSION

Development and optimize of chronomodulated drug delivery systems ofalbuterol sulphate.

Time controlled pulsatile release tablets (TCRTs) were prepared by coating Theophylline &Albuterol Sulphate containing core tablets with EC/HPMC in different ratio. The blend for compression proved good flow and compression properties as determined by Angle of repose, Carr's index and Hausner's ratio. Drug excipient compatibility study revealed no drug-polymer interaction determined by physical observation for one month at stored at accelerated stability condition (40 ± 2 °C/75 ±5% RH), DSC and FTIR study. Core tablets containing 5% CCS and 10% HPMC was found to be suitable for time controlled pulsatile release tablets.

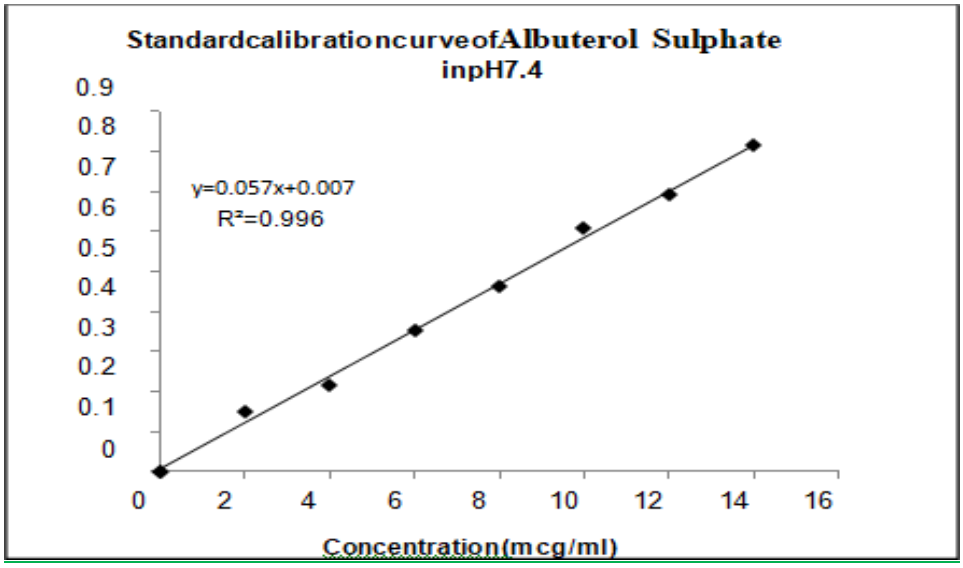

Figure 1: Calibration curve of Albuterol Sulphate in pH 7.4buffer

Table 1: Albuterol Sulphate calibration data in pH 6.8 and 7.4 buffer

SR.No.	Concentrationn (µg/ml)	Average Absorbance at680nm
1	2	0.129
2	4	0.252
3	6	0.401
4	8	0.517
5	10	0.682
6	12	0.760
7	14	0.885

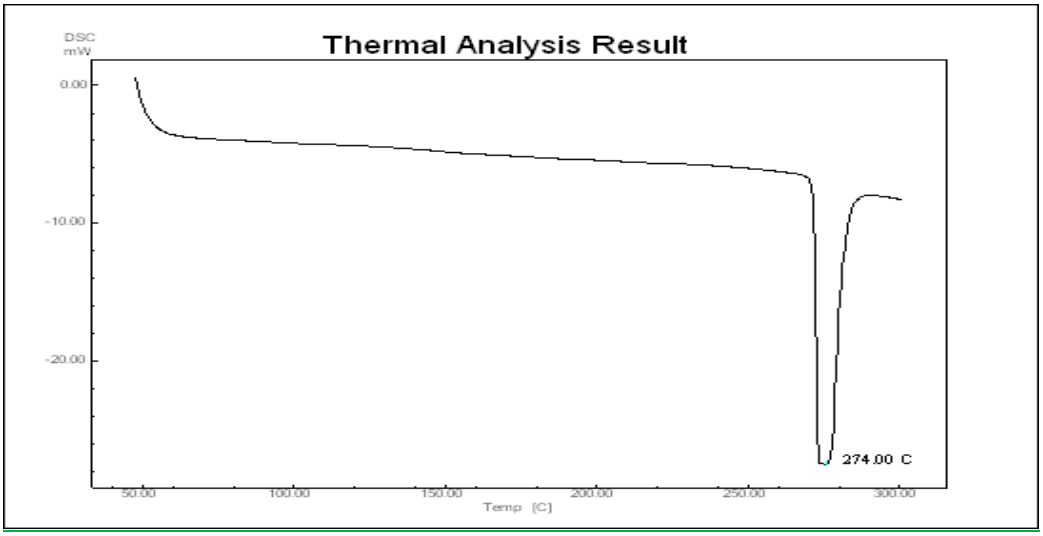

Figure 2: the DSC thermograms of theophylline

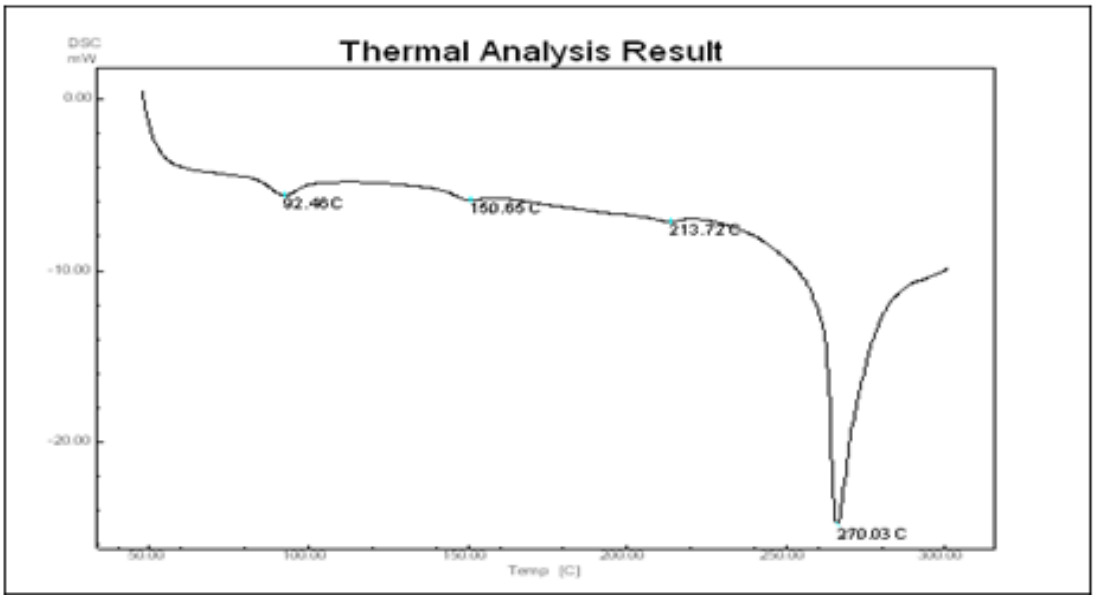

Figure 3: DSC thermogram of mixtureof theophylline and excipients.

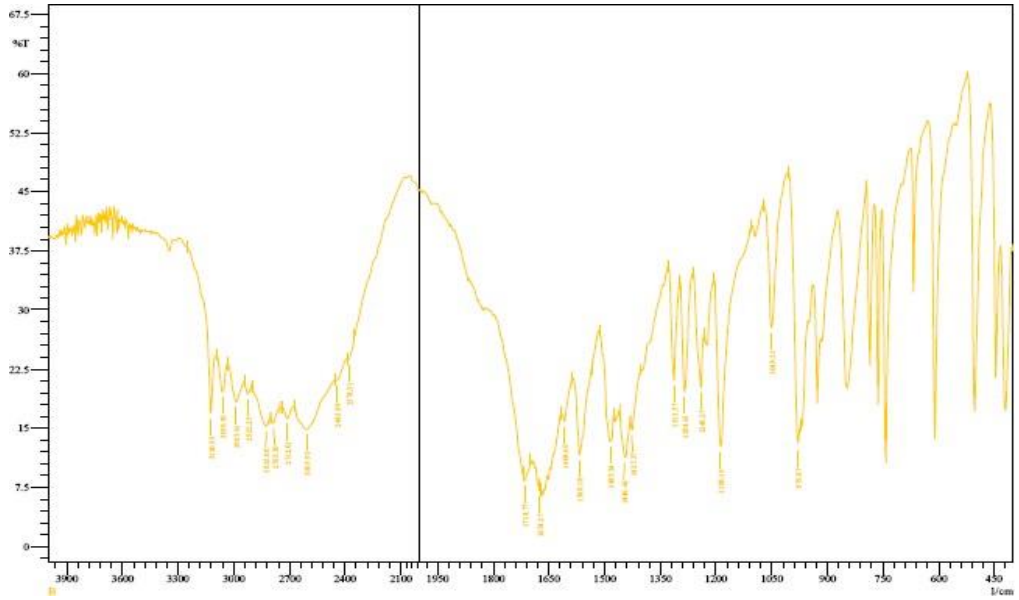

Figure 4: FTIR spectra of theophylline drug and excipient mixture

Table 2: Composition of Theophylline core tablets

Sr No	Ingredients	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)	P5 (mg)
1	Theophylline	400	400	400	400	400
2	Crosscarmellose Sodium	20	22	24	26	30
3	Aerosil	4.0	4.0	4.0	4.0	4.0
4	Lactose	23	21	19	17	13
	BINDER SOLUTION					
5	PVPK-30	3.0	3.0	3.0	3.0	3.0
6	Isopropyl alcohol	Q.S	Q.S	Q.S	Q.S	Q.S
Total weight		450	450	450	450	450

Table 3: Micromeritic properties of different formulation blends of Albuterol Sulphate

Batch No.	Angle of Repose (°)	Carr's Index (%)	Hausner Ratio
P-1	22.35	16.10	1.34
P-2	24.12	15.36	1.26
P-3	23.45	15.28	1.28
P-4	24.62	18.23	1.27
P-5	25.48	19.14	1.25

Table 4: Formulation details of Albuterol Sulphate pellet

SrNo	Ingredients	P1 (mg)	P2 (mg)	P3 (mg)	P4 (mg)	P5 (mg)
1	Albuterol sulphate	28.00	28.00	28.00	28.00	28.00
2	Lactose monohydrate	60	58	57	55	59
3	Microcrystalline cellulose(Avicel PH 101)	49	49	49	49	49
4	Hypromellose (HPMC 5cps)	25	27	28	30	26
5	Purified water*	Q.S	Q.S	Q.S	Q.S	Q.S
Pellets coated with Eudragit® RS 30D						
5	Eudragit® RS 30D	25	25	25	25	25
6	Talc	6.50	6.50	6.50	6.50	6.50
7	Triethyl Citrate	6.50	6.50	6.50	6.50	6.50
8	Purified water*	QS	QS	QS	QS	QS
Total weight		200	200	200	200	200

Table 5: Mean drug content (%) of Albuterol Sulphate pellets

Evaluationparameter	Formulation code				
	P1	P2	P3	P4	P5
Drug content (%) (mean)	83.21	82.26	88.85	84.33	0.11
± SD	± 2.52	± 0.41	± 0.06	± 0.82	± 1.11
RSD (%)	2.69	0.45	0.07	0.86	1.22

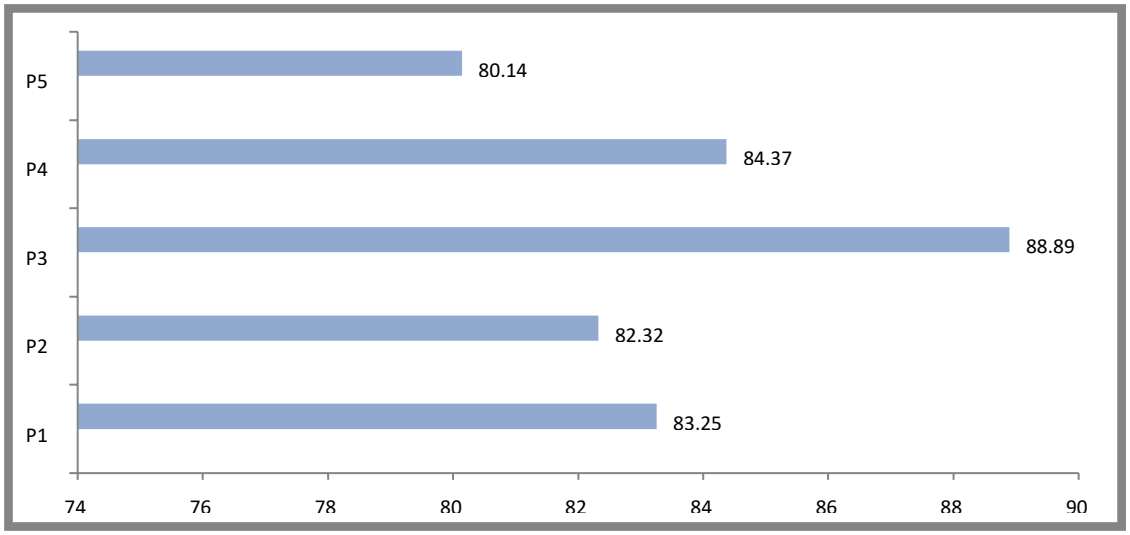

Figure 5: Bar graph representation of mean Drug content (%) ofpellets

Table 6: In-vitro release profile (CPR%) of Albuterol Sulphate in pH 1.2

Media	Time (mins)	Cumulative Percentage Release (CPR %) ±SD				
		P-1	P-2	P-3	P-4	P-5
pH1.2	0	0	0	0	0	0
	15	39.52 ±0.21	32.54 ± 1.45	22.07 ± 1.38	32.69 ±3.27	20.45 ± 0.13
	30	73.74 ±1.28	54.66 ±3.14	49.33 ± 2.87	62.10 ±4.67	35.76 ± 1.16
	45	91.67 ±4.76	62.58 ±1.23	69.59 ± 2.12	83.32 ±1.12	59.68 ± 3.78
	60	-	81.34 ± 3.22	88.34 ± 0.78	-	83.34 ± 2.55
	75	-	-	-	-	-

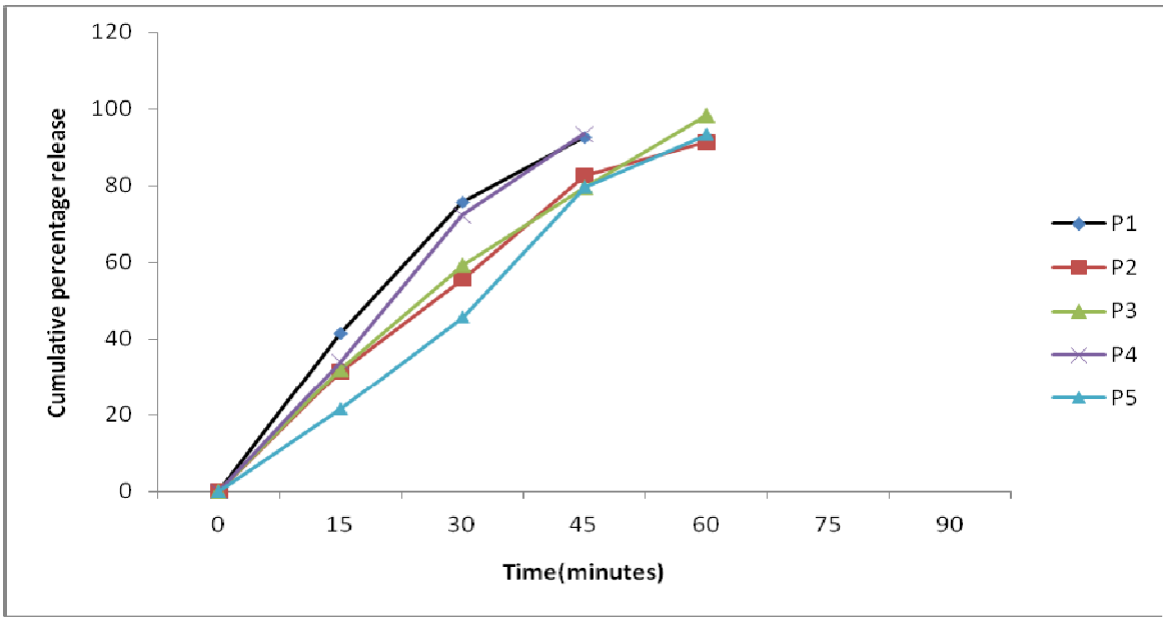

Figure 6: Comparative In-vitro release profile (CPR %) of Albuterol Sulphate pellets in pH 1.2

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