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RESEARCH ARTICLE

FORMULATION AND EVALUATION OF CONTROLLED RELEASE MATRIX TABLET OF ALBUTEROL SULPHATE

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ABSTRACT

A sustained release matrix formulation for Albuterol Sulphate was designed and developed to achieve a 12 h release profile. Using HPMC K15M and HPMC K100M as an inert matrix forming agent to control the release of Albuterol Sulphate. The matrix tablets for these formulations were prepared by direct compression and their in-vitro release tests were carried out for a period of 12 hours using USP dissolution test apparatus (type II Paddle) at 37±0.5°C and 50 rpm speed. A 3^2 full factorial design was used for optimization by taking the concentration of HPMC K15M (X1) and HPMC K100M (X2) were selected as independent variables, whereas initial release at the (Y1, % drug release), (Y2, % drug Content) the concentration of Were chosen as dependent variables. The optimized formulation F9 follows Higuchi model and Korsemeyer - Pappas release kinetics with non- Fickian diffusion mechanism. From the study, it was concluded that the release of Albuterol Sulphate can be effectively controlled using combination of HPMC K15M, HPMC K 100M and Carbopol 940.

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INTRODUCTION

Salbutamol Sulphate is a β-2 adrenergic agent with more bronchodilator effect and is useful in the treatment of asthma. Salbutamol Sulphate must be dosed three to four times a daily to maintain its bronchodilation effect due to the short half-life is 4-6 hrs. Further, asthmatic patients require continuous drug therapy for a long period. It can be achieved through controlled release systems. Therefore, to reduce the frequency of administration and to improve patient compliance, a once daily sustained release formulation of salbutamol Sulphate is desirable. The drug is freely soluble in water, and hence judicious selection of release retarding excipients is necessary to achieve a constant in- vitro input rate of the drug. The most commonly used method of modulating the drug release is to include it in matrix system. Hydrophilic polymer matrix systems are widely used in oral controlled drug delivery to obtain a desirable drug release profile, cost effectiveness, and broad regulatory acceptance. Therefore an attempt has been made to develop controlled release drug delivery system of Salbutamol Sulphate by formulating, matrix tablets using hydroxy propyl methyl cellulose, Gelucire43/01 and Carbopol 940. The matrix system is the most widely used controlled release delivery system of rapidly released drugs. The drug is uniformly dispersed or dissolved in suitable polymeric materials. Matrix tablets are the type of controlled drug delivery systems, which release the drug in continuous manner by dissolution control as well as diffusion controlled mechanisms. To control the release of the drugs, which having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials. One of these least complicated approaches to the sustained release dosage forms involves the direct compression of blend of drug release, retardant material and additives to formulate a tablet in which the material and additives to formulate a tablet in which the drug embedded in a matrix of the release retardant. To Control the release of the drug, which are having different solubility properties, hydrophilic and hydrophobic matrices have been used. For water soluble drugs, the hydrophobic and hydrophilic polymeric matrices are mixed.

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Table 1. Composition of tablet as per Factorial Design (All values are expressed in mg)

Ingredients	Formulation code								
Quantity(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Albuterol Sulphate	08	08	08	08	08	08	08	08	08
Gelucire 43/01	24	24	24	24	24	24	24	24	24
Microcrystalline cellulose	184	179	174	174	169	164	164	159	154
HPMC K15	15	20	25	15	20	25	15	20	25
HPMC K100	10	10	10	20	20	20	30	30	30
Carbopol 940	5	5	5	5	5	5	5	5	5
Aerosil	8	8	8	8	8	8	8	8	8
Magnesium Stearate	3	3	3	3	3	3	3	3	3
Talc	3	3	3	3	3	3	3	3	3
Total	260	260	260	260	260	260	260	260	260

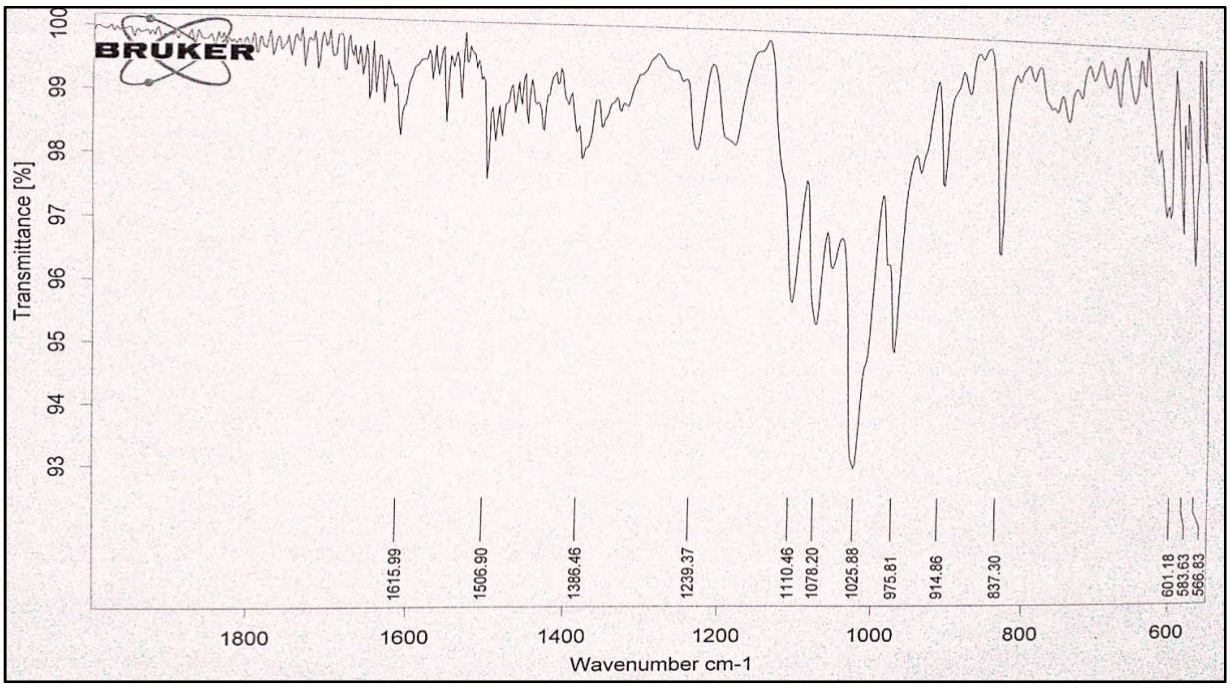

Figure 1. FTIR spectrum of Albuterol Sulphate

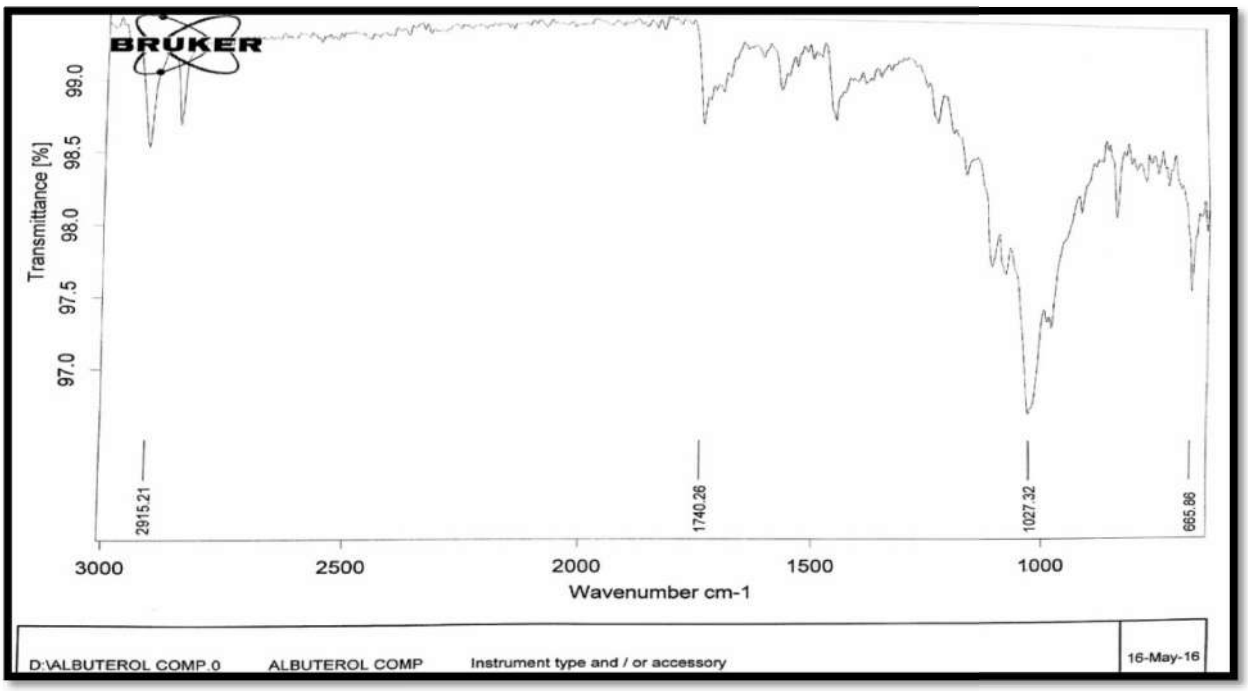

Figure 2. FTIR spectrum of physical mixture of Albuterol Sulphate

Hydrophobic material such as alcohols, acids and esters are mixed with ingredients and compressed. In an approach the slow release drug particles are prepared and mixed with hydrophobic materials and then compressed (Reddy *et al*., 2003; Goodman and Gilman's the pharmacological basis of therapeutics, 2001).

MATERIALS AND METHODS

Albuterol sulphate was procured as gift sample from FDC Limited, Aurangabad. Gelucires gift sample from Gattefossé Chemicals Mumbai. HPMC K15M and HPMC K100M were procured as sample from signet chemicals. Other chemicals and solvents were of analytical grade and which were provided by R.G. Sapkal College of pharmacy, Nashik.

Experimental Work

Preparation of controlled release tablet of Albuterol Sulphate

Controlled release matrix tablets of albuterol sulphate (F1 to F9) were prepared by developing the formulate using variable concentrations of different polymer HPMC K 100M, HPMC K 15M, Carbopol 940 as shown in table 1. The concentration of Albuterol sulphate was kept constant for all batches of formulations (Gattefose).

All the above formulations were prepared as per the above composition and subjected for compression.

Steps in the preparation of Albuterol Sulphate by Melt Method

1. Gelucires 43/01 was heated to form a molten base at53°C i.e. 10°C above the melting point 43°C on water bath.
2. Albuterol Sulphate was added to this molten base with continuous stirring.
3 The obtained mixture was then subjected to rapid cooling to solidify in a freezer for 24 h.
4 These solid mixtures were then screened sequentially through 20, 40 & 60 mesh sieves.

Manufacturing process of Albuterol Sulphate tablet

- **Step 1:** Albuterol Sulphate and Gelucires 43/01 granules of different ratios prepare with melt method were weighed accurately and mixed with MCC DC and sifted through 40# mesh.
- **Step 2:** HPMC K15M, HPMC K100M and Carbopol were weighed accurately and mixed then sifted through 40# mesh.
- **Step 3:** Mix in the mixture of Albuterol Sulphate granules and MCC DC (step with mixture of HPMC K15M, HPMC K100M and Carbopol(step 2) and sifted through 40# mesh.
- **Step 4:** MCC DC and Aerosil were weighed accurately, mixed and sifted through 40# mesh.
- **Step 5:** Talc and magnesium stearate were weighed accurately, mixed and sifted through 60# mesh.
- **Step 6:** Mix the mixtures of step 3, step 4 and step 5. The accurately weighed powder were then subjected to direct compression to form a Albuterol Sulphate tablet by using 8mm on Rotary tablet minipress-I (Rimek, Karnavati Engineering Ltd., Mehsana, Gujarat) (Bharathi *et al*., 2011; El-Bagory *et al*., 2012).

Precompression Studies (Lachman *et al*., 2009; Chein, 2002)

Bulk density

The bulk density was obtained by dividing the mass of powder by the bulk volume. The sample equivalent to 5 g was accurately weighed and filled in a 10 mL graduated cylinder and the powder was leveled and the unsettled volume, (V_0) was noted. The bulk density was calculated by the formula

$$Bulk\ density\ (\rho_0) = \frac{M}{V_0}$$

Where, ρ_0 = Bulk density,
M = Mass of powder taken and
V_0 = Apparent unsettled volume.

Tapped density

The tapped density was determined by mechanically tapping the measuring cylinder or by using the digital bulk density tester and the tapped volume was noted. The tapped density was calculated by the formula

$$Tapped\ density\ (\rho_0) = \frac{M}{V_t}$$

Where, ρ_t = tapped density,

M = weight of powder and
V_t= tapped volume of powder in cm^3.

Hausner's ratio

Hausner ratio gives an idea regarding the flow of the blend. It is the ratio of tapped density to the apparent density. Hausner's ratio was calculated as

$$Hausnerratio = \frac{Bulk}{Tapped}$$

Compressibility index

The compressibility index measures of the propensity of powder to be compressed. The packing ability of drug was evaluated from change in volume, which is due to rearrangement of packing occurring during tapping (USP, 2006). It is indicated as cars compressibility index (CI) and can be calculated as follows:

$$CompressibilityIndex = \frac{Tapped \quad Bulk}{Tapped} \times 100$$

Angle of repose

Funnel method: Funnel with a sound stem of 20 to 30 mm diameter was attached to the burette stand the height of which was adjusted such that its tip just touches the apex of powder. The graph paper sheet was placed below the funnel. The powder was allowed to flow through the funnel freely onto the surface of the graph paper sheet. Circle was marked around the heap covering approximately 90% of total powder bed. Procedure was repeated thrice to obtain the average reading & average diameter.

$$tan\theta = \frac{h}{r}$$

Where h = height if the powder pile and
r = radius of heap.

Postcompression Studies (Fiese and Hagen, 2009; The Indian Pharmacopeia.6thed)

Hardness

Although hardness test is not an official test, tablet should have sufficient handling qualities during packing and transportation. Hardness of tablet was measured using Monsanto hardness tester. It is the pressure required to fracture diametrically placed tablets by applying force. The hardness of randomly selected 6 tablets, from each batch was determined and means hardness was taken into account, which was expressed in kg/cm^2.

Thickness

All tablets were subjected for thickness measurement by using digital vernier caliper. All the measurements were made in triplicate.

Friability

Friability is the measure of tablet strength. This test subjects a number of tablets to the combined effect of shock abrasion by utilizing a plastic chamber which revolves at a speed of 25 rpm for 4 minutes, dropping the tablets to a distance of 6 inches in each revolution.

Method

For the friability test sample of 10 whole tablets were selected randomly. All tablets were dedusted carefully and weighing accurately the required number of tablets were placed in the drum and rotated about 100 times. Tablets were removed from the drum and loose dust was removed from the tablets, weighed accurately. The percentage weight loss should not be more than 1% of the total weight.

$$Friability = \frac{initial\ weig\ t \quad final\ weig\ t}{initial\ weig\ t} \times 100$$

Uniformity of weight

20 units were selected at random and were weighed individually, and average weight was calculated. Not more than 2 of the individual weight of tablets should deviate from the average weight by more than 5%.

Drug content (Assay)

Twenty tablets were weighed and average weight was calculated. The 20 tablets were crushed to obtain fine powder. Tablet powder equivalent to 9.68 mg of Albuterol Sulphate was transferred to 100 mL volumetric flask; diluted to a mark with 0.1 N HCL and sonicated for 10 min. The resulting solution was filtered through Whatman filter paper and filtrate was appropriately diluted with 0.1 N HCL. And the absorbance is measured at 276 nm.

In vitro dissolution studies of Matrix tablet

Dissolution study of Albuterol Sulphate (The United State Pharmacopeia, 2008)

The test is designed to determine compliance with the dissolution requirement for solid dosage forms administered orally.

Apparatus: 2 (Paddle)

Medium: 900 ml of 0.1 N HCL

Speed: 50 rpm.

Times: 1, 2, 4, 8, 9, and 12 hours.

Temperature: 37^0c.

Tablet was placed in jar containing 900ml of 0.1 N HCL for 12 hours and samples at different time interval 5ml of aliquots were removed and filtered through whatman filter paper no.52 at time interval specified (1, 4, 8, and12 hours.) and analyzed by UV-Visible spectroscopy at 276 nm and 0.1 N HCL as blank.

Dissolution kinetic study

Various mathematical models like; Zero-order model, First-order model, Higuchi (Matrix) model and Korsmeyer-Peppas Model were evaluated with respect to the dissolution profiles of the optimized formulations.

RESULTS AND DISCUSSION

Infra-red spectrum of Albuterol sulphate is shown in figure no.10. The major peaks observed and corresponding functional groups are given table no.31. Infra- red spectrum shows peak characteristic of structure of Albuterol Sulphate.

Compatibility Study

Fourier Transform Infra-red Spectroscopy

Infra- red spectra of physical mixture showed matching peaks with the drug spectra. The characteristic peaks of drug were also present in the spectra of all drug- polymer combinations. A spectrum of physical mixture is shown in figure.

Table 2. Evaluation of Powder Bulk for Tablets

Formulation code	Angle of repose(θ°) Mean± S.D	Bulk density (gm/cm^3) Mean± S.D	Tapped density (gm/cm^3) Mean± S.D	Compressibility index (%) Mean± S.D	Hausner's ratio Mean± S.D
F1	27.73±0.0115	0.3488±0.0033	0.4080±0.006	13.82±0.173	1.16±0.01
F2	29.72±0.097	0.3431±0.0019	0.4116±0.004	15.43±0.208	1.18±0.011
F3	32.2±0.0854	0.3273±0.0019	0.3761±0.0045	11.72±0.17	1.14±0.015
F4	30.74±0.075	0.3292±0.0070	0.3871±0.00743	12.45±0.05	1.18±0.012
F5	31.41±0.01677	0.3424±0.0024	0.4076±0.0041	14.14±0.005	1.13±0.0115
F6	30.47±0.0568	0.3471±0.0017	0.4079±0.0036	11.97±0.2764	1.17±0.0173
F7	29.91±0.0650	0.3382±0.0016	0.4013±0.001	15.38±0.0577	1.14±0.0288
F8	32.06±0.0556	0.3389±0.0054	0.3783±0.0039	13.24±0.0288	1.13±0.040
F9	30.42±0.0230	0.3447±0.0064	0.4077±0.0028	12.66±0.017	1.18±0.057

Table 3. Evaluation of Albuterol sulphate tablet

Formulation Code	Average Weight (mg) Mean ± S.D	Weight variation %	Hardness (kg/cm$^{2)}$ Mean± S.D	Thickness (mm) Mean± S.D	Friability (%) Mean± S.D	Drug content (%) Mean± S.D
F1	259.2±0.8027	0.0357	4.51±0.015	4.07±0.005	0.384±0.016	99.93±0.614
F2	258.1±0.4818	0.6701	4.21±0.015	4.12±0.0057	0.462±0.012	98.12±0.782
F3	258.1±0.4333	0.0357	4.32±0.049	4.08±0.0057	0.462±0.012	98.07±0.974
F4	258.1±0.5859	0.6928	4.41±0.01	4.01±0.0057	0.577±0.016	98.44±1.170
F5	258.5±0.5	0.6642	4.63±0.015	4.05±0.020	0.423±0.020	99.01±0.538
F6	258.3±0.5972	0.0007	4.21±0.005	4.14±0.0057	0.423±0.016	98.90±0.815
F7	257.7±0.3306	0.0357	4.10±0.005	4.10±0.0057	0.385±0.012	98.62±0.678
F8	258.7±0.5587	0.0714	4.11±0.02	4.11±0.0057	0.423±0.012	98.52±0.763
F9	258.4±0.8055	0.3928	4.15±0.208	4.14±0.01	0.385±0.008	99.01±0.517

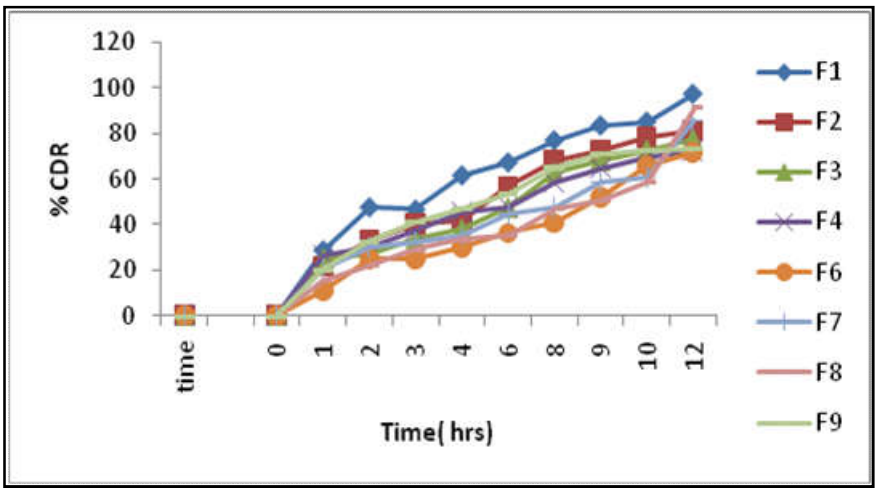

Figure 3. Cumulative Drug Release of Formulations (F1 to F9)

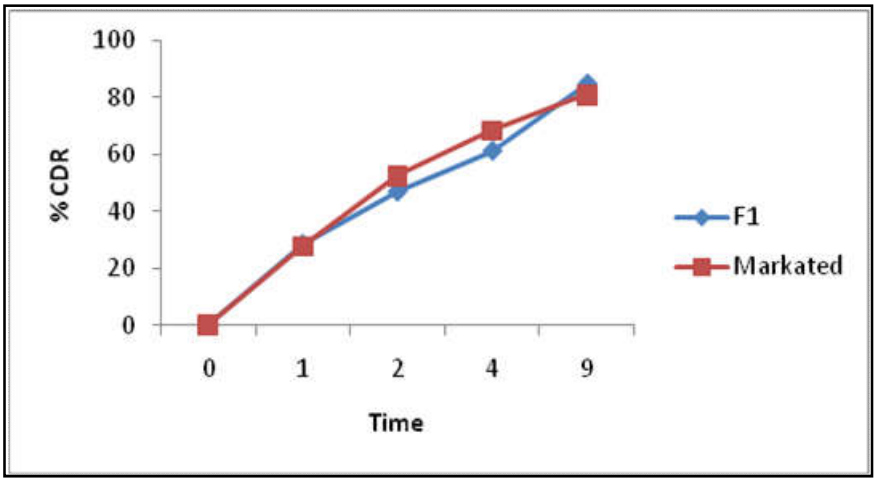

Figure 4. Comparative dissolution of Albuterol Sulphate tablet with that of Marketed formulation

Evaluation Studies

All batches of prepared bulk powder were evaluated for various parameters like precompression studies and prepared tablet were evaluated for various parameters like hardness, friability, content uniformity and in vitro dissolution studies. The result of all batches of prepared tablets of Albuterol Sulphate for different parameters viz. hardness, friability, and content uniformity are shown in table

Pre compression study

Many types of angular properties have been employed to assess flow ability, of these; angle of repose is the most relevant. Angle of repose of the powder was investigated. The value of Angle of repose (θ°) decreased after the addition of lubricant. Angle of repose (θ°) is an indicative parameter of powder flow ability from hopper to die cavity. The angles of repose of all the formulations were within the range of 27°–30° indicative of excellent and good flow ability. Bulk density may influence compressibility, tablet porosity, dissolution and other properties and depends on the particle size, shape and tendency of particles to adhere together. The bulk density of powder was found to be between 0.33-0.35 gm/cm^3. The values indicates good packing capacity of granules. The tap density of the granules of factorial design batches were found in the range of 0.37-0.40gm/cm^3. The bulk density and tap density was used to calculate the percent compressibility of the powder. The compressibility index of the Powder was observed in range of 11 to 15, indicating good compressibility of the granules. The values of the Hausner's ratio were found to be in the range of 1.11 to 1.18 indicating good and fair flow ability. Data is summarized in.

Post compression study

All the prepared tablet formulations were subjected to compendial test for post compression evaluation such as friability, hardness, thickness, uniformity of weight and content uniformity results obtained for the same are given in table. All tablets were found in the given in official compendia for the test such as friability, uniformity of weight, and drug content.

In-Vitro dissolution study of Albuterol sulphate tablet

Dissolution studies of Albuterol sulphate tablet from each other determined by UV method. The best batch of Albuterol sulphate tablet was selected on the basis of in vitro drug release to prepare tablet. In vitro dissolution study of the formulation containing polymer in different concentration were compared. Albuterol Sulphate tablet formulation F1 to F9 contains 1:3 ratio of Albuterol Sulphate: Gelucire 43/01 granules. Batch F1 to F9 contained the 1: 3 ratio of Albuterol sulphate: Gelucire 43/01 granules and HPMC K100M and HPMC K15M were used in the concentration of 10 to 30 % and 15 to 25% with respect to the average weight of the tablet. F 1 batch drug release for 1st, 4th, 8th, and 12th hours were found to be within the specification limit given in USP. And other batches they are release rate are increase then these batches are not release rate as per USP limit specification but F 1 batch are dose dumping in 11th and 12thhrs are 95.30%. Then these batch are optimized as per in vitro dissolution study.

Comparison of best formulation

The promising formulations F1 as found by evaluation studies were compared with marketed tablet. The marketed formulations showed drug release up to 12 hrs whereas selected formulations (F1) controlled release formulation drug release upto 12 hr and has better control over drug release rate. The respective release profile of marketed formulation and selected formulations indicated that the drug release performance of F1 is rather better controlled than the marketed formulations.

Dissolution kinetic study

To analyze the mechanism of drug release from the tablet, data obtained from the drug release studies was subjected to different mathematical models (Zero order, First order, Matrix (Higuchi) and Korsmeyer's Peppas). The correlation coefficient (r^2) was used as an indicator for the best fitting for each of the models. Table shows the Kinetics treatment for the optimized formulations.

Table 4. Model fitting of Optimize Batch of Albuterol Sulphate formulation

Code	Zero order	1st order	Higuchi	Peppas	
				R^2	n-Value
F9	0.713	0.7704	0.9064	0.8319	0.0511

Summary and conclusion

The present research work was carried out to develop a matrix tablet of albuterol sulphate. In this Albuterol sulphate as a controlled release was prepared by using combination of hydrophilic and hydrophobic matrix polymers such as HPMC K100M, HPMC K15M and Gelucire 43/01. Albuterol Sulphate are indicated for the treatment β2-adrenoreceptor agonist and bronchodilator. Albuterol Sulphate is highly water soluble drug. The plasma half-life of Albuterol Sulphate is 4- 6 hours. And dosing frequency of tablet is more than once per day. Hence it is suitable candidate for design of controlled release drug delivery system. Controlled release matrix tablet of Albuterol sulphate was prepared using Gelucire 43/01 and all batches of Albuterol sulphate were subjected to dissolution testing. Drug release from the matrix was found to decrease with increase in polymer concentration. F1 batch was show the drug release as per specification given in USP. Therefore the F1 batch was selected among all batches of Albuterol sulphate. Different polymers were employed in order to formulate matrix tablet of drug. Different drug: polymers ratios for tablet were employed as 1:3, 1:7, were prepared by two methods as direct compression method and melt method. The final tablet was formulated using optimized batch Albuterol Sulphate i.e. F1 respectively. The final matrix tablet formulation (F1) complied with the internal specification for weight variation, thickness, hardness, friability, drug content and in vitro drug release. The optimized formulation was compared with market

product and showed better result as that of marketed formulation. From the R^2 value it was concluded that the drug release profile of reproducible batch of Albuterol sulphate followed Highuchi release pattern.The drug release kinetics of the optimized tablets correspond best to Higuchi model and the drug release mechanism of Albuterol sulphate as per n value was found to be anomalous (nonficksian) diffusion and super case II transport respectively.After the stability study it was observed that stability batch showed no significant change in physical appearance, drug content or in vitrodissolution pattern after storage at 40±2°C / 75±5%RH for 3 months.

Conclusion

In conclusion, the results of the present study indicate that the release of a hydrophilic drug from a matrix tablet formulation is primarily affected by the ratio and the type of the polymer and secondarily by the direct compression method. Above studies successfully demonstrated the use combination of lipophilic (Gelucire 43/01) and hydrophilic (HPMC K15M, HPMC K100M) polymer were effectively controlled release of Albuterol Sulphate up to 12 hours and show the drug release as per specification given in USP. From the FT-IR and DSC characterization it can be concluded that the Albuterol Sulphate was compatible with the polymers used in formulation of matrix tablet. The final tablet was formulated using optimized batch of Albuterol sulphate i.e. F1respectively which shows better drug release when compared with market product. No significant change was observed in physical appearance, drug content and in vitro drug release before and after stability studies for 3 months (ICH Harmonised Tripartite Guideline, 2003). Hence, it is finally concluded that, the matrix tablet technology can be successfully applied for Controlled release of Albuterol sulphate.

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