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Formulation development and evaluation of controlled release matrix tablets of guaiphenesin and salbutamol sulphate

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ABSTRACT

In the present study controlled-release matrix tablets of Guaiphenesin and Salbutamol Sulphate were prepare and evaluated by using Na CMC, Xanthan gum, HPMC100cps, Ethyl Cellulose (15cps), Compritol, Precirol in different concentrations for treatment of respiratory disorders. Various tablet formulations were prepared and evaluated for compatibility studies and physical parameters such as Hardness, Friability, Dissolution, Content Uniformity and Thickness. The manufacturing procedure was optimized with respect to the thickness between 6.3 to 6.5mm, hardness 5 to 6 kg/cm^2 and description being white, oval shaped tablets with break line on one side. The tablet weight was targeted for 800mg. The developed formulations showed uniform pre and post compresssional properties. Out of all formulations F5 was showed higher rate of drug release 105.49 & 113.62 for Guaiphenesin and Salbutamol Sulphate respectively when compared to other formulations. Formulation containing NaCMC, Xanthan gum, HPMC100cps polymers showed higher rate of drug release over a period of 24hrs. In conclusion, the results suggest that the developed sustained-release matrix tablets of Guaiphenesin and Salbutamol Sulphate is a potential attempt, and better than conventional dosage forms, leading to avoid dosing frequency and better patient compliance.

Keywords: Guaiphenesin, Salbutamol Sulphate and Respiratory disorders.

INTRODUCTION

Sustained release, sustained action, prolonged action, controlled release , timed release , depot dosage forms are terms used to identify drug delivery systems that are designed to achieve prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. Conventional dosage forms give up drug to surrounding tissues or fluids at a time varying rates that are highest initially and decline continuously thereafter. The primary consideration or objective in clinically treating pathological /physiological disorders in the attainment and maintenance of a predetermined plasma drug

concentration (minimum effective concentration, MEC) in the body for the said amount of time. Hence, the saw tooth pattern of the drug delivery of conventional pharmaceutical dosage forms and its reflection both on drug concentration in body fluids and drug effects is simply a result of the limited functionality of traditional dosage forms, which have two major effects on therapeutics[13]. They are

- Requirements of frequent drug administration encouraging patient non compliance with the regimen, and
- Inability to use drugs having short half life.

The rapid growth of polymer technology, its application to solutions of some biomedical problems and extensive research in better understanding of its action, its mechanism of drug absorption and tissue levels have led to the development of an entirely new class of pharmaceutical dosage forms, the "controlled release dosage forms", which deliver drugs with good precision. Being a class of controlled release dosage forms, sustained release dosage forms also offers, many advantages [1]. [2]

Hence in the present study was undertaken to develop sustained release tablets containing Guaiphenesin and Salbutamol Sulphate for treatment of respiratory disorders and also for better patient compliance.

MATERIALS AND METHODS

Salbutamol Sulphate and Guaiphenesin as a gift sample (Zydus Cadila Healthcare Ltd, Bangalore).Ethyl cellulose100cps and 15cps, HPMC 100 cps were obtained from colorcon asia private Ltd. Goa, India. Compritol, precirol were received from Gattefose Company. Lactose, Purified talc and Pottasium dihydrogen phosphate were purchased from E. Merck (India) Mumbai.

Table 1 : Formulation design – quantities shown in mg

Ingredients mg/tablet	F1	F2	F3	F4	F5
Guaiphenesin	600	600	600	600	600
Salbutamol Sulphate	4	4	4	4	4
Lactose	23	33	33	23	10
Sodium CMC	50	-	-	-	60
Xanthan Gum	50	-	-	-	50
HPMC (100cps)	40	50	75	-	40
HPMC (15M)	-	-	50	-	-
Ethyl Cellulose(100cps)	-	75	-	-	-
HPMC (K4M)	-	-	15	-	-
Ethyl Cellulose(15cps)	-	15	-	-	-
Compritol	-	-	-	40	-
Precirol	-	-	-	40	-
Glyceryl Monostearate	-	-	-	60	-
HPC LF (in IPA)	20	-	-	20	15
PVP K30(in IPA)	-	10	10	-	-
Purified Talc	4	4	4	4	3
Aerosil	3	3	3	3	2
Magnesium Stearate	6	6	6	6	6
Total in mg	800	800	800	800	800

Methodology:

Preparation of Matrix tablets of Guaiphenesin and Salbutamol Sulphate : The tablet dosage forms were formulated by using wet granulation method and the manufacturing procedure is as follows [3] [4]:

Formulation F1:

Step 1: Sifted Guaiphenesin, Salbutamol sulphate, Lactose Monohydrate, Sodium CMC, Xanthan gum, HPMC (100cps) through sieve # 40 separately. The integrity of the sieve was checked before and after sifting. Mixed Guaiphenesin, Lactose Monohydrate, sodium CMC, Xanthan gum, HPMC (100cps) in a poly bag for 15 minutes. Salbutamol Sulphate was added by geometrical dilution method.

Step 2: Preparation of binder solution and granules: Dissolved HPC LF in 15 ml of Isopropyl Alcohol, the binder solution was added to the sifted materials, mixed thoroughly with spatula until granules are formed. Granules were dried in air and in hot air oven (at 50°C) with intermittent mixing for 30 minutes. Loss on drying of the granules was checked in the halogen moisture analyzer. Dried granules were passed through sieve # 20.

Step 3: Lubrication and compression: Separately sifted Purified Talc, Colloidal Silicon Dioxide and Magnesium Stearate through sieve # 40 and mixed with the dried granules for 5 minutes in a poly bag and compressed into tablets using 19 x 8.8 mm punch containing break line.

Formulation F2:

Step 1: Sifted Guaiphenesin, Salbutamol Sulphate, Lactose monohydrate, Ethyl cellulose (100 cps), HPMC (100 cps) through sieve # 40 separately. The integrity of the sieve was checked before and after sifting. Mixed Guaiphenesin, Lactose Monohydrate, Ethyl cellulose (100 cps), HPMC (100 cps) in a poly bag for 15 minutes. Salbutamol sulphate was added by geometrical dilution method.

Step 2: Preparation of binder solution and granules: Dissolved Polyvinylpyrrolidone in 15 ml of Isopropyl Alcohol, the binder solution was added to the sifted materials, mixed thoroughly with spatula until granules are formed. Granules were dried in air and in hot air oven (at 50°C) with intermittent mixing for 30 minutes. Loss on drying of the granules was checked in the halogen moisture analyzer. Dried granules were passed through sieve # 20.

Step 3: Lubrication and compression: Separately sifted Ethyl cellulose (15cps), Purified Talc, Colloidal Silicon Dioxide and Magnesium Stearate through sieve # 40 and mixed with the dried granules for 5 minutes in a poly bag and compressed into tablets using 19 x 8.8 mm punch containing break line.

Formulation F3:

Step 1: Sifted Guaiphenesin, Salbutamol sulphate, Lactose monohydrate, HPMC (100 cps), HPMC (15 cps) through sieve # 40 separately. The integrity of the sieve was checked before and after sifting. Mixed Guaiphenesin, Lactose Monohydrate, HPMC (100 cps), HPMC (15 cps) in a poly bag for 15 minutes. Salbutamol sulphate was added by geometrical dilution method.

Step 2: Preparation of binder solution and granules: Dissolved Polyvinylpyrrolidone in 15 ml of Isopropyl Alcohol, the binder solution was added to the sifted materials, mixed thoroughly with spatula until granules are formed. Granules were dried in air and in hot air oven (at 50°C) with intermittent mixing for 30 minutes. Loss on drying of the granules was checked in the halogen moisture analyzer. Dried granules were passed through sieve # 20.

Step 3: Lubrication and compression: Separately sifted HPMC K4M, Purified Talc, Colloidal Silicon Dioxide and Magnesium Stearate through sieve # 40 and mixed with the dried granules for 5 minutes in a poly bag and compressed into tablets using 19 x 8.8 mm punch containing break line.

Formulation F4:
Step 1: Sifted Guaiphenesin, Salbutamol Sulphate, Lactose monohydrate, Compritol, Precirol through sieve # 40 separately. The integrity of the sieve was checked before and after sifting. Mixed Guaiphenesin, Lactose Monohydrate, Compritol, Precirol in a poly bag for 15 minutes. Salbutamol Sulphate was added by geometrical dilution method.

Step 2: Preparation of binder solution and granules: Dissolved Hydroxy propyl cellulose LF in 15 ml of Isopropyl Alcohol, the binder solution was added to the sifted materials, mixed thoroughly with spatula until granules are formed. Granules were dried in air and in hot air oven (at 50°C) with intermittent mixing for 30 minutes. Loss on drying of the granules was checked in the halogen moisture analyzer. Dried granules were passed through sieve # 20.

Step 3: Lubrication and compression: Separately sifted Glyceryl mono stearate, Purified Talc, Colloidal Silicon Dioxide and Magnesium Stearate through sieve # 40 and mixed with the dried granules for 5 minutes in a poly bag and compressed into tablets using 19 x 8.8 mm punch containing break line.

Formulation F5:
Step 1: Sifted Guaiphenesin, Salbutamol sulphate, Lactose monohydrate, Sodium CMC, Xanthan gum, HPMC (100 cps) through sieve # 40 separately. The integrity of the sieve was checked before and after sifting. Mixed Guaiphenesin, Lactose Monohydrate, Sodium CMC, Xanthan gum, HPMC (100 cps) in a poly bag for 15 minutes. Salbutamol Sulphate was added by geometrical dilution method.

Step 2: Preparation of binder solution and granules: Dissolved HPC LF in 15 ml of Isopropyl Alcohol, the binder solution was added to the sifted materials, mixed thoroughly with spatula until granules are formed. Granules were dried in air and in hot air oven (at 50°C) with intermittent mixing for 30 minutes. Loss on drying of the granules was checked in the halogen moisture analyzer. Dried granules were passed through sieve # 20.
Step 3: Lubrication and compression: Separately sifted Purified Talc, Colloidal Silicon Dioxide and Magnesium Stearate through sieve # 40 and mixed with the dried granules for 5 minutes in a poly bag and compressed into tablets using 19 x 8.8 mm punch containing break line.

Evaluation of pre compression parameters of granules:

Bulk density [5]**:** Bulk density was determined (Konark instruments, India) by placing a fixed weight of granules (100 G) blend in a measuring cylinder on bulk density testing unit (Konark Instruments, India) and the total volume was noted. Bulk density was calculated by using the formula.

Bulk density = Total weight of granules / Total volume of granules

Average of three densities of granules were taken and tabulated. (n=3)

Tapped density [5]**:** Tapped density was determined in a bulk density testing apparatus (Konark instruments, India) by placing the granules in the measuring cylinder and the total volume of granules was noted before and after 100 tappings.

Tapped density was calculated by using the formula.

Tapped density = Total weight of granules / Total volume of granules after 100 tappings

Average of three densities of granules were taken and tabulated. (n=3)

Compressibility index [6]**:** Compressibility index was determined by placing the granules in a measuring cylinder and the volume (V_0) was noted before tapping. After 100 tapping again volume (V) was noticed.

Compressibility index = $(1- V/ V_0) \times 100$

V0 = volume of granules before tapping.
V = volume of granules after 100 tappings.

Average of three compressibility indices of granules readings were taken.

Angle of repose (^{0}ø) [7]**:** Angle of repose was determined by measuring the height and radius of the heap of the granule bed. A cut stem funnel was fixed to a stand and bottom of the funnel was fixed at a height of 3 cm from the horizontal plane. Granules was placed in the funnel and allowed to flow freely. With the help of vernier calipers (Mitutoyo, Japan) the height and radius of the heap were measured and noted. Average of triplicate readings was computed (n = 3).

$\tan ø = h / r$

h = height of heap of granule bed.
r = radius of heap of granule bed.

Evaluation of post compression parameters of tablets:

Friability Test [8]**:** Twenty tablets were weighed and tested for friability in the Roche friabilator.

Hardness Test [9]**:** Three tablets were taken for testing of hardness and tested using Pharma test apparatus and Monsanto hardness tester.

Thickness [9]**:** Three tablets were taken for measuring the thickness.

Weight variation [10]**:** Twenty tablets were weighed and subjected to weight variation test. Weight variation tolerances are based on the average tablet weight and the pharmacopoeial requirement is that not more than two tablets out of twenty would differ from the average weight more than +/- 5% and none of the twenty tablets would differ by more than 120% from the average weight.

Content Uniformity [3]**:** Five tablets from each formulation were crushed separately and dropped in five volumetric flasks separately, added 50ml of water and kept in sonicator for five minutes after the complete dissolution, flasks were removed and added sufficient water to make up the volume 100ml. Solution was filtered through Whatman filter paper, from this one ml was withdrawn and made upto 100ml with distilled water and analyzed by the HPLC for drug content

Physical appearance: Physical appearance of a tablet involves the measurement of a number of attributes such as tablet size, Shape. Colour, presence or absence of odour, Taste, Surface texture, Physical flaws and legibility of any identifying marking [10] [14]**:**.

***In vitro* Dissolution of Sustained release tablets containing Guaiphnesin and Salbutamol Sulphate by HPLC:** The *in vitro* dissolution study of tablets was performed using USP 1 apparatus fitted with basket (rpm 50) at temperature: 37°C ± 0.5°C using distilled water (900ml) as a dissolution medium. Sampling volume: 10 ml sampling interval: Every 2 hours upto 12 hours and 24th hour and samples were analyzed at 273nm (guaiphnesin) and 276nm (salbutamol Sulphate) by HPLC method to calculate the percentage dissolved [11] [12].

Standard preparation: Weighed accurately about 600 mg Guaiphenesin and Salbutamol sulphate into a 100 ml volumetric flask. Added 50 ml of water sonicated for 5 min to dissolve and made upto volume with the same. Diluted 1 ml of this solution to 10 ml with mobile phase.

Sample Preparation: Placed 900 ml of medium preheated to 37°C in the dissolution vessel. Fixed the shaft to their respective positions. Six individual tablets were weighed and dropped into the basket. Fixed all baskets to their respective shafts and operated the dissolution for 24 hours. At the end of every 2 hours withdrew about 10 ml of sample midway between surface of medium and the basket from each of the six jars. Filtered the sample through Whatmann filter paper no # 1. Diluted 1 ml of this solution to 10 ml with the mobile phase in each case. Measured the area of standard and the samples at 276 nm for Salbutamol Sulphate, Guaiphenesin and calculated for percentage dissolved[15].

RESULTS AND DISCUSSION

From the above results, it was observed that the Friability was within 0.5%, which was well within the specifications (not more than 1.0%).The thickness of tablets was found to be within

limits of In-house specifications. The hardness was maintained between 5.0-5.5 kg/cm^2. The weight variation was found to comply with Pharmacopoeia. (±5.0% from the average weight).

Table 2: Pre compression parameters data

Active Ingredients	Description	Solubility	Melting Point	Bulk density	Tapped density	Hausner ratio	%Amt in collector	Moisture content in %	Hygros-copicity
Guaiphene-sin	Complies as per IP/USP	Complies as per IP/USP	78°C	0.392	0.588	1.50	1.64	0.2%	0.59
Salbutamol sulphate	Complies as per IP/USP	Complies as per IP/USP	157-158°C	0.351	0.426	1.2	1.5	0.1%	0.3

Table 3: Weight variation

Lot. No	Weight of 20 tablets	Avg wt	Label claim (gms)	
			Guaifnecin	Salbutamol sulphate
F1	16.00	0.798	0.600	0.004
F2	15.77	0.783	0.600	0.004
F3	15.65	0.786	0.600	0.004
F4	15.70	0.779	0.600	0.004
F5	16.00	0.804	0.600	0.004

Table 4: Finished Product Evaluation results

Parameters	F1	F2	F3	F4	F5
Hardness (kg/cm^2)	5.5	5.0	5.0	5.5	5.0
Thickness (mm)	6.55	6.73	6.68	6.56	6.5
Friability (%w/w)	0.33	0.40	0.46	0.28	0.35

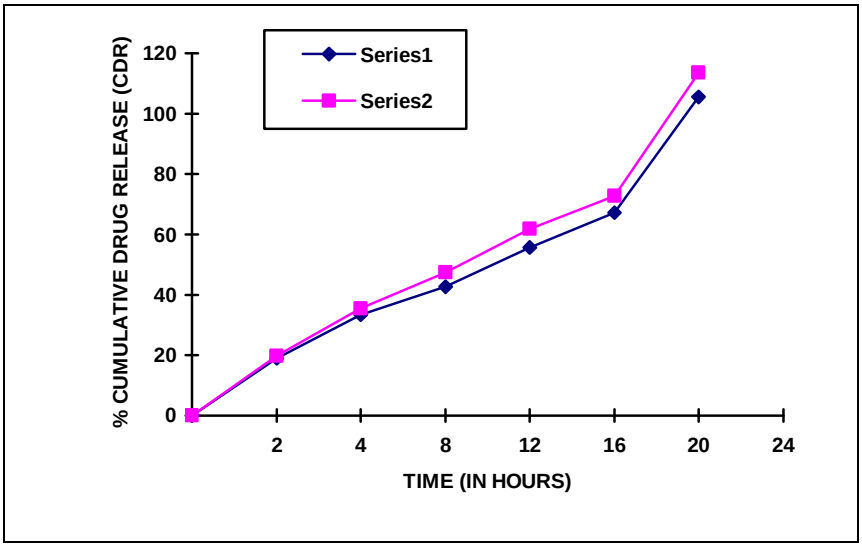
Table 5: Weight variation test for five batches

Lot No	Weight variation			Limits (5% of avg. wt.)		% RSD
	Avg. Wt. (mg)	Min. wt. (mg)	Max. wt. (mg)	Min (mg)	Max (mg)	
F1	798.1	781.5	804.6	758.3	837.9	0.6048
F2	796.3	793.5	800.0	756.5	836.06	0.240
F3	796.1	787.9	800.0	756.6	835.8	0.312
F4	788.9	788.9	798.1	749.1	828.9	0.3453
F5	794.5	794.5	800.9	755.2	835.0	0.352

Table 6 : Content Uniformity results by HPLC

Samples	Guaiphenesin (%)	Salbutamol Sulphate (%)
F1	98.49	98.68
F2	66.79	67.83
F3	72.17	73.16
F4	99.706	98.26
F5	97.21	92.63

Dissolution Profile of F1: Guaiphenesin and Salbutamol Sulphate sustained release tablets. The dissolution was carried out for 5 batches of prepared sustained release tablets. The percentage drug dissolved for 24 hours shown in the table 11, 12, 13, 14 & 15.



Series 1: Salbutamol Sulphate, Seires 2: Guaiphenesin

Fig. 1: Dissolution profile for F5 - Trial 1

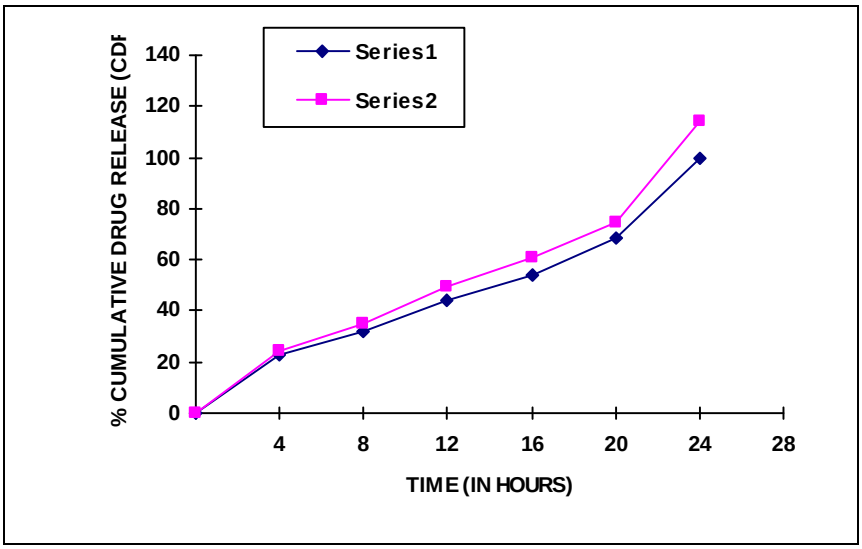


Fig. 2: Dissolution profile for F5 - Trial 2

Summary and Conclusion: The present work was an attempt to formulate sustained release tablets of Salbutamol Sulphate and Guaiphenesin. The work is summarized and concluded in the following section. Salbutamol Sulphate and Guaiphenesin are bronchodilator, expectorant respectively. These drugs need to be administered for extended periods for respiratory disorders. These drugs are administered repeatedly to sustain the plasma concentrations within the therapeutic range. To reduce frequency of administration and yet remain therapeutically successful, it was formulated as sustained release formulation.

Preformulation study: In the preformulation studies, three drugs were studied for their pharmacopoeial compliance. The approved drugs were studied for their pharmaceutical characteristics.

Table 7: Dissolution Profiles of tablet formulations

Formula	Time in hrs	2 hrs	4 hrs	6 hrs	8 hrs	10 hrs	24 hrs
F1	Salbutamol sulphate (%)	32.3	42.62	60.98	68.19	73.97	113.59
	Guaiphenesin (%)	29.16	46.72	60.41	74.75	85.75	123.06
F2	Salbutamol sulphate (%)	45.49	55.70	73.21	76.19	87.34	95.55
	Guaiphenesin (%)	37.34	49.21	66.62	77.61	87.49	115.17
F3	Salbutamol sulphate (%)	41.59	59.52	69.46	76.22	90.95	105.72
	Guaiphenesin (%)	29.85	46.68	61.77	69.95	80.27	117.83
F4	Salbutamol sulphate (%)	52.63	66.95	75.02	80.63	83.63	111.7
	Guaiphenesin (%)	44.78	60.91	73.29	82.14	89.44	119.48
F5 (Trial 1)	Salbutamol sulphate (%)	18.96	33.31	42.61	55.71	67.25	105.49
	Guaiphenesin (%)	19.75	35.46	47.44	61.94	72.83	113.62
F5 (Trial 2)	Salbutamol sulphate (%)	22.79	32.04	44.16	53.98	68.43	99.55
	Guaiphenesin (%)	24.61	34.77	49.46	60.78	74.44	114.39

From sieve analysis, it can be concluded that drugs were fine powders, as 88% of the powder passed through # No. 100. All the three drugs were non-hygroscopic in nature. The melting point of the drugs was as per pharmacopoeial standards.

Formulation & Evaluation: Five formulations were prepared and evaluated with respect to their physical parameters such as hardness, friability, dissolution, content uniformity and thickness.

Out of five formulations, F5 was found to be the best formulation with respect to dissolution/ release of all the drugs in the tablets. Formulation containing Sodium CMC, Xanthan gum & HPMC 100 cps as polymers showed release of the drugs over a period of 24 hours. The manufacturing procedure was optimized with respect to the thickness between 6.3 – 6.5 mm, hardness between 5.0 to 6.0 kg/cm^2 and description being white, oval shaped tablets, with breakline on one side. The tablet weight was targeted for 800 mg.

Stability studies: Among all five formulation F5 was the best, and hence charged for stability studies at 25°C, 60% RH 30°C, 65% RH and 40°C, 75% RH.

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