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FORMULATION, DEVELOPMENT AND EVALUATION OF FAST DISSOLVING DRUG. LEVOSALBUTAMOL TABLETS

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Abstract

Asthma symptoms are the result of bronchial hyperresponsiveness, bronchospasm, and chronic airway inflammation. Short-acting, inhaled beta2 agonists; oxygen; intravenous fluids; and corticosteroids are the mainstays of treatment for acute exacerbations. The R-enantiomer of albuterol is responsible for bronchodilation. The S-enantiomer exhibits broncho-constricting activity in vitro, which may be mediated by muscarinic receptors and may be opposed by adding the anticholinergic agent ipratropium bromide. Levalbuterol improves pulmonary function to a greater extent than racemic albuterol and reduces the need for costly hospitalizations in patients with acute asthma exacerbations.

It was estimated that more than 339 million people suffer from asthma. Asthma is the most common noncommunicable disease among children. Most deaths occur in older adults.

Under Preformulation study, the physicochemical properties were complied with the IP and USP specification. Physical properties such as appearance, melting point, effect of temperature and humidity in different conditions were more in Levosabutamol raw powder. Parameters evaluated were within the USP limit.

The compatibility evaluations were performed by FTIR spectroscopy. The observation implies that the drug and polymers were compatible with each other. There were no interaction found between polymers and drug.

The formulations were evaluated on the basis of Pharmacopoeial specification visual appearance, pH, drug content, Hardness, Friability, Disintegration test, assessment of drug release, release kinetics were carried out as per specifications and results were found to be complied with the Pharmacopoeial specification.

INTRODUCTION

1.1 Asthma

Asthma is a major non-communicable disease characterized by recurrent attacks of breathlessness and wheezing, which vary in severity and frequency from person to person. Symptoms may occur several times in a day or week in affected individuals, and for some people become worse during physical activity or at night. During an asthma attack, the lining of the bronchial tubes swell, causing the airways to narrow and reducing the flow of air into and out of the lungs. Recurrent asthma symptoms frequently cause sleeplessness, daytime fatigue, reduced activity levels and school and work absenteeism. Asthma has a relatively low fatality rate compared to other chronic diseases.

1.2 Fast dissolving drug delivery system

The concept of fast dissolving drug delivery system emerged from the desired to provide patient with conventional means of taking their medication. Fast dissolving dosage form can be disintegrated, dissolved or suspended by saliva in mouth. The fast dissolving tablets disintegrates instantaneously when placed on tongue and releases the drug, dissolve or disperses in saliva. The fast dissolving tablets are useful in patients like pediatric, geriatric, bedridden or mentally disabled, who may face difficulty in swallowing conventional tablet or capsule leading to ineffective therapy 5 , most pharmaceutical forms for oral administration are formulated for direct ingestion or for chewing or for prior dispersion/dissolution in water. Some of them are absorbed in mouth (sublingual or Buccal tablet) to obviate the problem associated with conventional dosage forms orally fast dissolving tablets have been developed which combine hardness, dosage uniformity, stability and other parameters, since no water is required for swallowing the tablets and they are thus suitable for geriatric, pediatric and travelling patients.

The demand for Fast Dissolving Tablets (FDTs) has been growing during the last decade especially for elderly and children who have difficulties in swallowing. Levosalbutamol (LVS) is the R-enantiomer of short acting β2-adrenergic receptor.

The fast dissolving tablet formulation is defined by the food and drug administration (FDA) as, “A solid dosage form containing medicinal substances which disintegrates rapidly, usually within matter of seconds, when placed upon the tongue”. It is difficult for many patient to swallow tablets and hard gelatin capsule hence they do not comply with prescription, which results in high incidence of non-compliance and ineffective therapy. Such problem can be resolved by mean of fast dissolving tablet. These FDT are

designed to dissolve or disintegrates rapidly in saliva generally within 60second.

Tablet is most popular among all dosage forms existing today because of its self-administration, and easy manufacturing; however in case of hand tremors, dysphasia geriatric patients the problem of swallowing is common which leads to poor patient compliance. To overcome these drawbacks, mouths dissolving tablets or orally disintegrating tablets have emerged as alternative oral dosage form. These tablets disintegrate, dissolve and disperse in saliva within few seconds. Fast dissolving tablets are useful in patients like paediatric, geriatric, bed ridden or mentally disabled.

1.2.1 Desired criteria for mouth disintegration drug delivery system

Not require water to swallow, but it should dissolve or disintegrate in the mouth in a matter of seconds. Have a pleasing mouth feel.

Should compatible with masking.

Should be potable without fragility concern.

Exhibit low sensitivity to environmental condition such as humidity and temperature.

Allow the manufacturing of tablet using conventional processing and packaging equipment at low cost.

Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed. So, combines advantage of solid dosage form in terms of stability and liquid dosage form in terms of bioavailability.

1.2.3 Super disintegrants:

Disintegrants are agents added to tablet (and some encapsulated) formulation to promote the breakup of the tablet (and capsule "slugs') into smaller fragments in an aqueous environment thereby increasing the available surface area and promoting a more rapid release of the drug substance. They promote moisture penetration and dispersion of the tablet matrix. In recent years, several newer agents have been developed known as "super disintegrants'. These newer substances are more effective and mechanical strength. On contact with water, the super disintegrants swell hydrate, change volume or form and produce a disruptive change in the tablet.

Effective super disintegrants provide improved compressibility, compatibility and have no negative impact on the mechanical strength of formulation containing high-dose drugs. Tablet disintegration has received considerable attention as an essential step in obtaining fast drug release. The emphasis on the availability of drug highlights the importance of the relatively rapid disintegration of tablet as a criterion for ensuring uninhibited drug dissolution behavior. Number of factors affects the disintegration behavior of tablets. The development of fast dissolving or disintegration tablets provides an opportunity to take an account of tablet disintegrates. Recently new materials termed as super disintegrant have been developed to improve the disintegration process. Selecting appropriate formulation excipients and manufacturing technology can obtain the design feature of fast disintegrating tablet. The disintegrates have the major function to oppose the efficiency of the tablet binder and the physical forces that act under compression to form the tablet

The stronger the binder, the more effective must be the disintegrating agents in order for the tablets to release its medication. Ideally, it should cause the tablet to disrupt, not only into the granules from which it was compressed, but also into powder particles from which the granulation was prepared. Disintegrants are an essential component to tablets formulation. While rapidly disintegrating tablets do not necessarily ensure fast bioavailability, slowly disintegrating tablets assure slow bioavailability. The ability to interact strongly with water is essential to disintegrant function. Combinations of swelling and/or wicking and/or deformation are the mechanisms of disintegrant action. Super disintegrants offer significant improvements over starch. But hygroscopicity may be a problem in some formulation, a disintegrant used in granulated formulation processes on more effective if used both "intra-granularly' and "extra-granularly" thereby acting to break up the tablet into granules and having the granules further disintegrant to release the drug substance into solution. However, the portion of disintegrants added intra-granularly (in wet granulation processes) is usually not as effective as that added extra-granularly due to the fact that it is exposed to wetting and drying (as part of the granulation process) which reduces the activity of the disintegrant. Since a compaction process does not involve its exposure to wetting and drying, the disintegrant used intra-granularly tends to retain good disintegration activity.

2. Metarial and Methods

2.1 MATERIAL:-

Levosalbutamol was received as gift sample by Cipla Ltd.Sikkim, Croscarmillose Sodium, Crosprovidone, Sodium Starch Glycolate, Microcrystalline cellulose, Magnesium stearate and Aerosil Corel PharmaChem, Ahmadabad, Aspartame used was procured from Sweetener India, Delhi, and other reagents and chemicals used were of analytical grade.

Table 1: Quantity of raw materials for preparation of Levosabutamol tablets.

Ingredient	F1	F2	F3	F4	F5	F6	F7	F8	F9
Levosalbutanol sulphate (mg)	2	2	2	2	2	2	2	2	2
Chitosan (mg)	15.50	20.30	30.10	50.0	31.00	31.20	31.30	31.50	31.60
HPMC (mg)	-	-	15.60	15.60	15.60	-	15.60	15.60	-
Xanthan Gum (mg)	-	-	15.50	15.50	-	-	15.50	15.50	15.60
Ethyl Cellulose (mg)	-	-	-	-	15.00	15.00	-	-	-
PVP K-30 (mg)	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
MCC (mg)	20.50	15.10	10.00	15.60	2.90	9.80	15.10	10.00	15.60
Magnisum stearate (mg)	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20	1.20
Talc(mg)	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80	0.80
Distilled water	qs	qs	qs	qs	qs	Qs	qs	qs	Qs

2.2 METHOD:-

Fast dissolving tablets of Aceclofenac were prepared by direct compression method. Pure drug and excipients were passed through # 60 No. mesh. Required amount of drug and excipients were taken for every formulation according Table No. 1.

The powdered drug, Mannitol and Lactose were mixed uniformly with continuous triturating using mortar and pestle. Then required quantity of super disintegrates and aspartame taken for each formulation and mixed, finally magnesium stearate and talc powder were added and mixed well.

The mixed blend of drug and excipients were compressed using 10 station tablet punching machine. (Shakti pharmaceuticals**)** 4 Mm punch. A Batch of 50 tablets of each formulation was prepared for all the designed formulation. Before the tablet preparation punch the mixture blend of all designed formulations were subjected to compatibility studies (IR) and pre-compression parameters like- Angle of repose, Bulk density, Tapped density, compressibility index, Hauser's ratio.

3. RESULT AND DISCUSSION

3.1 Preformulation study

3.1.1 Organoleptic properties

The Levosalbutamol was bitter in taste and white in color. It inferred the provided sample was Levosalbutamol.

3.1.2 Pre-compression parameters: Powder ready for compression containing drug and various excipients were subjected for precompression parameters (micrometric properties) to study the flow properties of granules, to achieve uniformity of tablet weight.

3.1.3 Angle of repose (Ɵ): The data obtained from angle of repose for all the formulations were found to be in the range of 27.60º and 29.30º. All the formulations prepared by all three methods showed the angle of repose less than 30º which reveals good flow property.**3.1.4 Bulk Density:** Bulk density (BD) and tapped density (TD) for the blend was performed. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.45 gm/cc to 0.66 gm/cc (direct compression method) respectively.

3.1.5 Carr's consolidation index: The result of Carr's consolidation index or compressibility index (%) for the entire formulation blend ranged from 16.00% to 19.60%
3.1.6 Hausner's ratio: Hansner's ratio of entire formulation showed between 1.20 to 1.48 indicates better flow properties

Table 2: Pre-compression parameters of direct compression method

Formulation Code	Angle of repose (ɵ)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's Ratio	Compressibility Index (%)
F1	28.02	0.50	0.65	1.20	16.00
F2	29.10	051	062	1.22	17.00
F3	28.02	0.45	0.60	1.25	16.10
F4	29.30	0.45	0.62	1.30	16.20
F5	28.65	0.53	0.70	1.29	16.80
F6	27.60	0.54	0.72	1.36	16.52
F7	29.00	0.62	0.61	1.40	18.20
F8	29.20	0.65	0.72	1.45	18.62
F9	28.20	0.66	0.74	1.48	19.60

Identification of drug by UV spectroscopy

The Levosalbutamol was identified by UV spectroscopy method. The Levosalbutamol exhibited maXimum absorption at 276 nm. This wavelengths was considered as λ_{max} for sample and all the observations by UV spectrophotometer to calculate the amount of drug were taken at this wavelength.

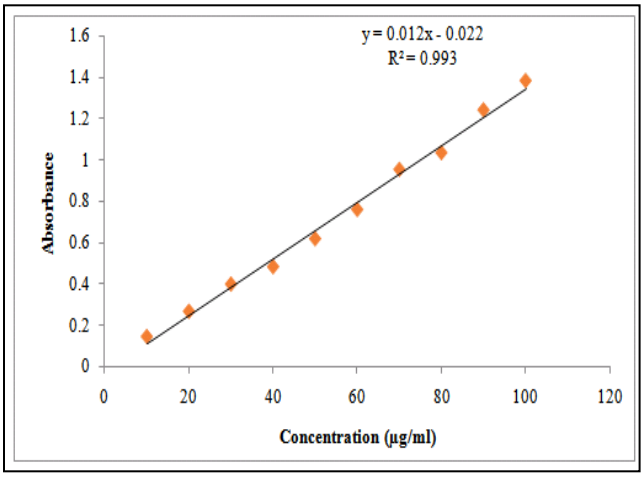
Standard curves of Levosalbutamol

The standard curves of Levosalbutamol were prepared in phosphate buffer pH 6.8 and 0.1 N HCl; The calibration curve was drawn for Levosalbutamol in pH 6.8 phosphate buffer, and it shows straight line in range of concentration from 10-100 µg/ml with R2 value of 0.993 which follows Beer-Lambert law Calibration curve of Flucytosine in 0.1 N HCl shows straight line in range of 10-100 µg/ml with R2 value of 0.9972 which follows Beer-Lambert law The outcomes inferred that Levosalbutamol produces higher

R2 value in 0.1 N HCl; it indicates better solubility in 0.1 N HCl.Levosalbutamolshowed good linearity in all the solution systems at a concentration range of 10-100 µg/ml

Table 3: Absorbance by Levosalbutamol drug at different concentration in pH 6.8 phosphate buffer

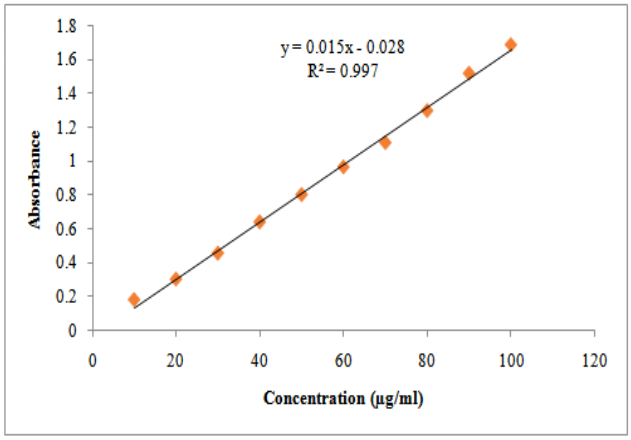
S. No.	Concentration in µg/ml	Absorbance at 276 nm
1.	10	0.147
2.	20	0.270
3.	30	0.398
4.	40	0.476
5.	50	0.610
6.	60	0.720
7.	70	0.940
8.	80	1.010
9.	90	1.231
10.	100	1.352



Graph 1: Calibration curve of Levosalbutamol drug in pH 6.8 phosphate buffer

Table 4: Absorbance by Levosalbutamol drug at different concentration in 0.1 N HCl

S. No.	Concentration in µg/ml	Absorbance at 276 nm
1.	10	0.180
2.	20	0.302
3.	30	0.441
4.	40	0.640
5.	50	0.801
6.	60	0.951
7.	70	1.210
8.	80	1.310
9.	90	1.510
10.	100	1.680



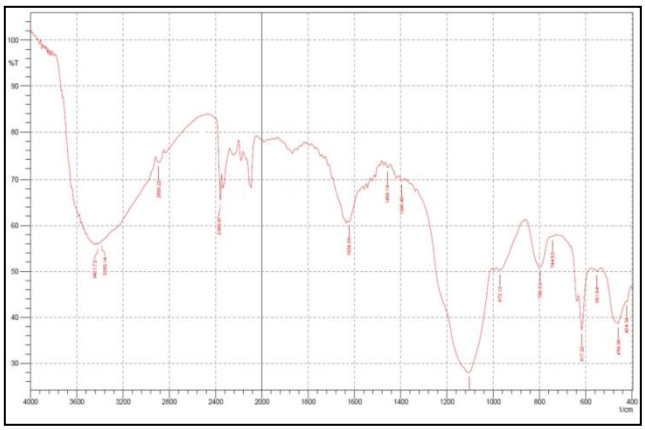
Graph 2: Calibration curve of Levosalbutamol drug in 0.1 N HCl

Identification of Levosalbutamol by FTIR

The spectra of FTIR indicate that the sample used was Levosalbutamol. The major peaks of Levosalbutamol are exhibited. The peaks displayed the functional group present in pure drug.

Table 3.6: Interpretation of FTIR spectra of Levosalbutamol

Wave number	Interpretation
3420.6	O-H, free hydroxyl group
2891.1	Aromatic C-H stretch
2361.7	Amine HCl N-H stretch
1622.1	C=O stretch
1395.3	C-H, bending
975.2	-CO, stretch
782.2	O-subtituted aromatic C-H out-of-plane deformation

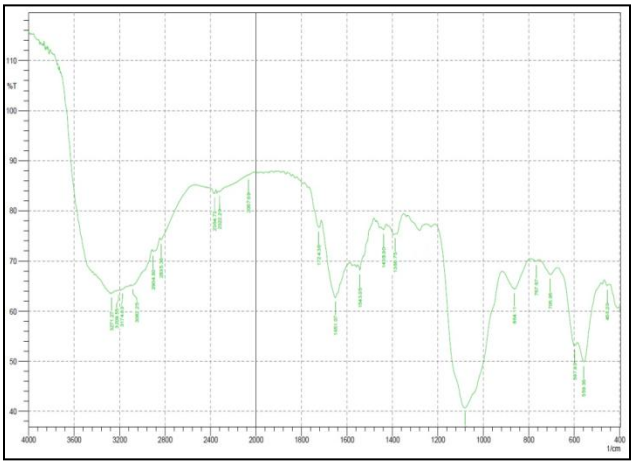


Graph 3: FTIR spectra of Levosalbutamol

Drug excipient compatibility studies

After performing FTIR of the Levosalbutamol and mixture of Levosalbutamol with excipients, it was found that the peaks obtained in drug mixture were in between the range

of main principle peaks and were found to be very near to previously performed FTIR of pure drug Levosalbutamol. No major deviation in peaks were obtained in IR spectra, hence this indicates that drug was compatible with other ingredients.



Graph 4: FTIR spectra of mixture of Levosalbutamol and excipients

3.2 Post-compression parameters:

3.2.1 Hardness:

The hardness of the tablets prepared was determined by Monsanto Hardness tester and found to be within the range of 2.5 kg/cm3 to 3.3kg/cm3.

3.1.2 Friability test:

The friability was found in all designed formulation in the range 0.36% to 0.44% to be well within the approved range (<1%)

3.1.3 Weight variation test:

The weight variation was found in all designed formulation in the range 199.6 to 203.1 mg and % deviation was in a range of 0.03 to 1.22. All the tablets passed weight variation test as the average percentage weight variation was within 7.5% i.e. in the pharmacopoeia limits.

3.1.4 Thickness:

The mean thickness was (n=3) almost uniform in all the formulations and values ranged from 4.52 mm to 4.65 mm. Standard deviation values indicated that all the formulations were within the range

3.1.5 Disintegration time:

The in-vitro disintegration time was measured by the time taken to undergo complete disintegration. Rapid disintegration within 3 minutes was observed in all the formulation. The disintegration time of all the formulation is checked & is found within the range of 15 Sec-20 Sec.

3.1.6 Wetting time:

Wetting time is closely related to the inner structure of the tablets. The wetting time of Levosalbutamol Sulphate tablets prepared were found to be in the range of 34-40 sec

3.1.7 Drug Content:

The uniform drug content was performed for all the formulations. The average value and standard deviation of the entire tablets were found to be in between 97.23 +1.26 to 100+1.84

3.3 In-vitro dissolution study:

Dissolution studies for all formulations were determined by USP type-II apparatus (DR-6, Campbell Instruments, Dissolution Test Apparatus 50 rpm). The dissolution profile of Levosalbutamol sulphate from the tablets was shown in Fig. 2, 3 & 4 at the time 30 min.

It was observed from the result that, CCS formulation showed maximum dissolution rate with more than 92.14% of drug released in 25 min.

CP formulation released more than 85.24% of drug release in 25 min and SSG formulation released more than 83.11% of drug release in 30 min.

Table 4: Post Compression parameter of tablets prepared by direct Method

Formulation Code	Hardness (kg/cm2)	Weight variation (mg)	Thickness (mm)	Wetting Time (in sec)	In-vitro Dispersion time (in sec)	Drug Content (%)	In-vitro Drug Release (%)	Friability (%)
F1	2.5	200	4.52	44	45	96.50	80.60	0.52
F2	2.6	198	4.58	43	49	95.60	85.60	0.54
F3	2.3	200	4.57	45	50	96.70	87.20	0.60
F4	2.0	197	4.60	46	56	99.50	90.00	0.51
F5	2.1	198	4.59	48	58	99.60	87.10	0.40
F6	2.0	200	4.58	44	60	98.50	88.20	0.35
F7	2.3	201	4.57	42	52	97.50	88.30	0.34
F8	2.7	199	4.58	41	56	99.40	88.34	0.30
F9	2.1	200	4.60	43	59	99.60	88.90	0.51

4. CONCLUSION

In present study, oral bioavailability of LS is around 40% this study results revealed that it is possible technique to enhance dissolution rate by using direct compression technique using different concentration as superdisintegrants three types of superdisintegrants in different concentration differed in their ability to disintegrate the Levosalbutamol Sulphate tablets.

The flow properties of recipients and drug were good. The tablets prepared were found to be good without any chipping, capping and sticking.

Formulated tablets gives satisfactorily result for various physicochemical evaluation in vitro dispersion time, wetting time, water absorption ratio and drug content.

FTIR studies revealed that there is no chemical interaction between Levosalbutamol sulphate and the excipients used in the study.

Formulated tablets gives satisfactorily result for various physicochemical evaluations of tablets like tablet dimension, hardness, friability and weight variation.

From the above study, F9 formulation was concluded as an optimized formulation due to its better disintegration time and better in-vitro dissolution profile. From the above data, it can be concluded that superdisintegrants croscarmillose sodium has better disintegrant property than other disintegrants namely, sodium starch glycolate and crospovidone.

In-vitro drug release of fast dissolving tablets of levosalbutmol sulphate was found to be in following order F9 > F3 > F2 > F7. Among all formulation F9 was to be the best formulation as it released 95.05% of drug, in 25 minutes. In comparison CCS is greater than CP and SSG.

The faster drug dissolution rate will lead to improve bioavailability, effective therapy, improve patient compliance and satisfies all the criteria as fast dissolving. The result concluded that fast dissolving tablet of levosalbutamol sulphate showing enhanced dissolution will improve bioavailability and effective therapy.

Effect of temperature and humidity in open & closed conditions

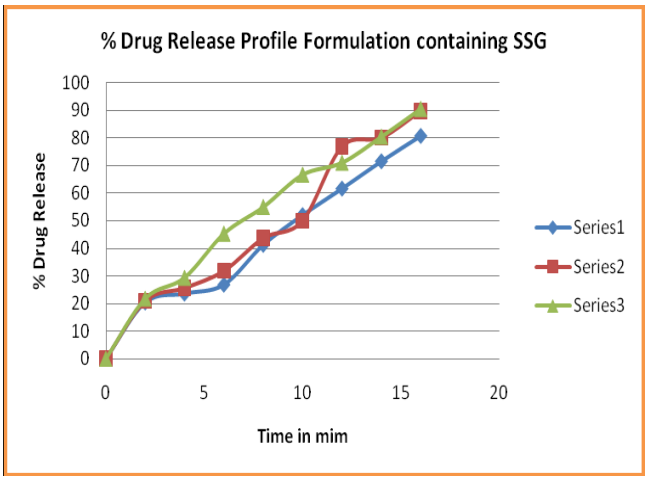
The drug–excipients compatibility was done at 25ºC/60% ± 5%,30ºC / 65% ± 5% relative and 40ºC/75% ±5% relative humidity. Opened and closed condition were used. The result doesn't show any physical change to the mixture after 4 weeks (Table 7.7 and 7.8). Chemical compatibility were analyzed by spectrum study. This fact concluded that the drug and excipients were compatible with each other.

Table 4: Effect of temperature and humidity in closed conditions

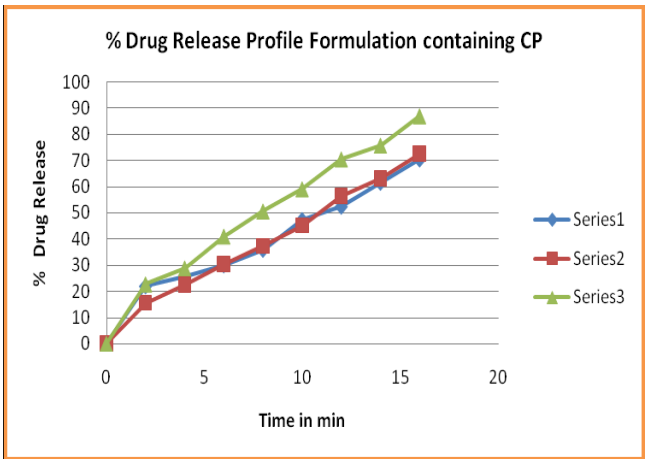
Drug	Observation				
Ingredients	Initial	25ºC /60% RH after 30days	30ºC /65% RH after 30Days	40ºC /70% RH after 30 days	Result
Levosalbutamol	White	White	White	White	Compatible
Levosalbutamol + Excipient	White	White	White	White	Compatible

Table 5: Effect of temperature and humidity in open conditions

Drug	Observation				
Ingredients	Initial	25ºC /60% RH after 30days	30ºC /65% RH after 30days	40ºC /70% RH after 30days	Result
Levosalbutamol	White	White	White	White	Compatible
Levosalbutamol + Excipient	White	White	White	White	Compatible



Graph 4: Profile of Formulation containing SSG (F1-F3)



Graph 5: Profile of Formulation containing CP (F4-F6)

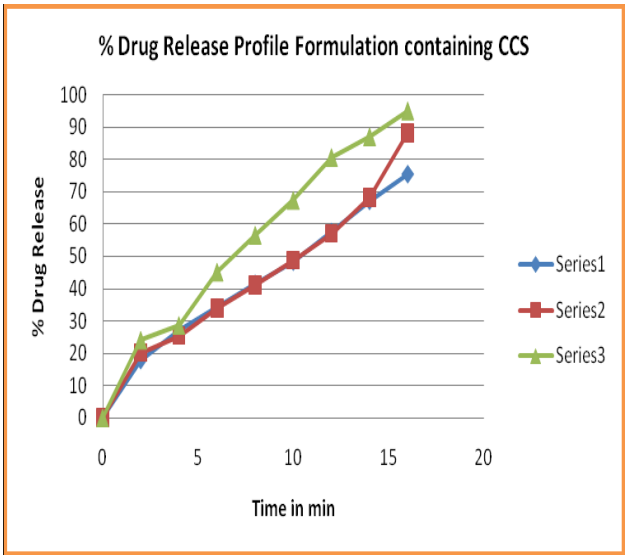
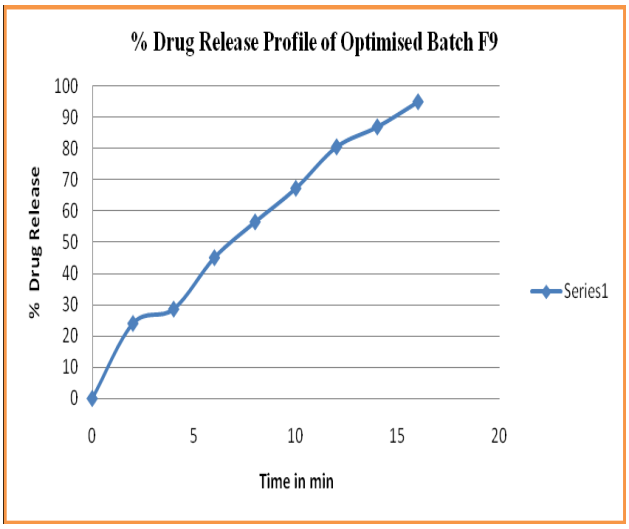


Figure 6: Profile of Formulation containing CCS (F7-F9)



Graph 6: Profile of optimized Formulation Batch F9

Table 2: Pre-compression parameters of direct compression method

Formulation Code	Angle of repose (ɵ)	Bulk density (g/cc)	Tapped density (g/cc)	Hausner's Ratio	Compressibility Index (%)
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F2	29.10	051	062	1.22	17.00
F3	28.02	0.45	0.60	1.25	16.10
F4	29.30	0.45	0.62	1.30	16.20
F5	28.65	0.53	0.70	1.29	16.80
F6	27.60	0.54	0.72	1.36	16.52
F7	29.00	0.62	0.61	1.40	18.20
F8	29.20	0.65	0.72	1.45	18.62
F9	28.20	0.66	0.74	1.48	19.60

Post Compression parameter of tablets prepared by direct Method

Formulation Code	Hardness (kg/cm2)	Weight variation (mg)	Thickness (mm)	Wetting Time (in sec)	In-vitro Dispersion time (in sec)	Drug Content (%)	In-vitro Drug Release (%)	Friability (%)
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F4	2.0	197	4.60	46	56	99.50	90.00	0.51
F5	2.1	198	4.59	48	58	99.60	87.10	0.40
F6	2.0	200	4.58	44	60	98.50	88.20	0.35
F7	2.3	201	4.57	42	52	97.50	88.30	0.34
F8	2.7	199	4.58	41	56	99.40	88.34	0.30
F9	2.1	200	4.60	43	59	99.60	88.90	0.51

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