GSC Biological and Pharmaceutical Sciences

eISSN: 2581-3250 CODEN (USA): GBPSC2

Cross Ref DOI: 10.30574/gscbps

Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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# Preparation and evaluation of salbutamol sulphate sublingual tablets

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GSC Biological and Pharmaceutical Sciences, 2025, 33(02), 065-070

Publication history: Received on 27 September 2025; revised on 03 November 2025; accepted on 06 November 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.33.2.0422

## Abstract

Aim of the present work was to prepare and evaluate sublingual tablets of salbutamol sulphate (SAL), for the treatment of asthma and COPD. Conventional SAL tablets available in the market are not suitable where quick onset of action is required. SAL sublingual tablets were prepared by using superdisintegrants like croscarmellose sodium, crospovidone, sodium starch glycolate by direct compression method using 8 mm punch. The prepared tablets were evaluated for postcompression parameters and *in vitro* drug release studies. Among all formulations F6 formulation was found to be the best as this formulation shown less disintegration time and possessing good tableting properties. An optimized tablet formulation i.e. F6 was found which provided short wetting time of 21 sec, *in-vitro* disintegration time of 149 sec which facilitates its faster disintegration and higher the drug content of 96.9%, the best *in-vitro* drug release was found to be in formulation F6 i.e. 97.69% during the end of 30min.

**Keywords:** Sublingual Tablets; Asthma; Crospovidone; Direct Compression

## 1. Introduction

Sublingual means “under the tongue”, the sublingual tablet is administered in such way that it gets rapidly disintegrate, dissolve in patient's mouth without chewing or water administration and absorbed rapidly through the blood vessels present below the tongue. Therefore, the drug gets enter into systemic circulation to give onset of action by avoiding the first pass metabolism and degradation. This route is most suitable for acid labile drugs and convenient for pediatrics, geriatrics, and psychiatric patients and also patients with difficulties in swallowing (dysphagia), and in situations where water is not available[1-3]. Whenever sublingual tablets put under tongue, it gives prompt outcome by empowering medication ingested rapidly via mucosal covering of mouth under tongue shown in figure 1. The medication assimilated from stomach goes to mesenteric flow which interfaces via portal vein. In this way assimilation through oral cavity stay away from primary pass digestion. The sublingual tablets are normally petite and uniform, compacted gently to maintain them subtle. Tablets must disintegrate rapidly permitting medication to be assimilated. It’s intended to disintegrate in modest salivation amount; after tablet is put in mouth beneath tongue, patient must not try not to eat, smoking, drinking and potentially talking to keep tablet set up. Systemic drug delivery via sublingual route had risen to give rapid beginning of pharmacological activity[3]. Sublingual items have been intended for quite a long time going from hypertension to psychological mal adjustment (depression and schizophrenia). Sublingual course gives time's more noteworthy assimilation of the medication than oral route and is out performed by hypodermic infusion[4-11]. SAL is the first selective short-acting $\beta_2$-agonist (SABA) used as an alternative reliever in the treatment of asthma. Its therapeutic effect is based on its potent smooth muscle relaxant properties, which allow the inhibition of bronchial smooth muscle contraction and subsequent bronchodilation [12]. In the present investigation an attempt is made to prepare salbutamol sulphate sublingual tablets for the treatment of asthma by using novel super disintegrating agents.

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## 2. Materials and methods

### 2.1. Materials

Salbutamol sulphate (SAL) active pharmaceutical ingredient was a gift from Sain medicaments Pvt ltd, Hyderabad., fructose, galen IQ, magnesium stearate was procured from S.D. Fine Chem-limited, Mumbai. Croscarmellose sodium (CCS), crospovidone (CP), microcrystalline cellulose (MCC) and sodium starch glycolate (SSG) were obtained from Arrow Chem Products, Mumbai.

### 2.2. Methods

*2.2.1. Preparation of sublingual tablets[13]*

Salbutamol sulphate sublingual tablets (SAL-SLTs) were prepared by the direct compression method using different concentrations of excipients viz., MCC (binding agent), mannitol (diluents), fructose (sweetening agent), CP, CCS and SSG (superdisintegrants) as per table 1. All the ingredients of the SAL-SLTs were weighed and mixed in mortar with the help of pestle. Then the blended material was slightly compressed on the 8 mm punch using a Cadmach rotary tablet machine. The total weight of the formulation was maintained 140 mg.

**Table 1** Formulae of SAL-SLTs

| **INGREDIENTS in mg** | **Formulations Batch size = 100 tablets** | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | F1 | F2 | F3 | F4 | F5 | F6 | F7 | F8 | F9 |
| SAL | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 | 4 |
| CCS | 4 | 8 | 12 | --- | --- | --- | --- | --- | --- |
| CP | --- | --- | --- | 4 | 8 | 12 | --- | --- | --- |
| SSG | --- | --- | --- | --- | --- | --- | 4 | 8 | 12 |
| PVP | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 | 20 |
| MCC | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Mannitol | 41 | 37 | 33 | 41 | 37 | 33 | 41 | 37 | 33 |
| Fructose | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Galen IQ | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| Magnesium stearate | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Talc | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| Total weight in mg | 140 | 140 | 140 | 140 | 140 | 140 | 140 | 140 | 140 |

*2.2.2. Evaluation[14-17]*

The prepared powder blend was subjected for precompression characteristics viz., bulk density, tapped density, compressibility index, flow properties (angle of repose). Sublingual tablets were evaluated for their post compression parameters i.e., thickness, diameter, weight variation, hardness, friability, wetting time, water absorption ratio and *in vitro* dissolution studies. All studies were carried out in triplicate and mean values were reported.

*2.2.3. In vitro dissolution studies*

*In vitro* drug dissolution studies were carried out for sublingual tablets by using 6.8 pH buffer as dissolution medium using 500 ml medium for 30 min withdrawal interval of 5min by using USP XXII dissolution apparatus type II (Campbell electronics, Mumbai). The drug release at different interval was measured at 224 nm using a double beam UV spectrophotometer. The study was conducted in triplicate and data were computed by using dissolution software PCP Disso V3.0.

## 3. Results

### 3.1. Precompression studies

The powder blend for tablets was prepared and subjected for precompression evaluation and results are given in table 2.

**Table 2** Precompression evaluation data

| Batches | Bulk Density (g/cm$^3$) | Tapped Density (g/cm$^3$) | Carr's Index | Hausner's Ratio | Angle of Repose θ |
|---|---|---|---|---|---|
| F1 | 0.44 ± 0.03 | 0.54 ± 0.01 | 18.51 ± 0.24 | 1.22 ± 0.24 | 27 ± 0.26 |
| F2 | 0.44 ± 0.09 | 0.50 ± 0.09 | 12.00 ± 0.15 | 1.13 ± 0.12 | 27 ± 0.30 |
| F3 | 0.41 ± 0.07 | 0.44 ± 0.03 | 6.81 ± 0.21 | 1.07 ± 0.16 | 28 ± 0.16 |
| F4 | 0.43 ± 0.01 | 0.49 ± 0.01 | 12.24 ± 0.17 | 1.13 ± 0.12 | 29 ± 0.12 |
| F5 | 0.42 ± 0.03 | 0.48 ± 0.03 | 12.5 ± 0.12 | 1.14 ± 0.11 | 29 ± 0.21 |
| F6 | 0.44 ± 0.03 | 0.46 ± 0.01 | 4.34 ± 0.29 | 1.04 ± 0.23 | 27 ± 0.20 |
| F7 | 0.41 ± 0.01 | 0.44 ± 0.03 | 6.81 ± 0.32 | 1.07 ± 0.02 | 26 ± 0.23 |
| F8 | 0.41 ± 0.03 | 0.45 ± 0.03 | 8.88 ± 0.21 | 1.09 ± 0.16 | 27 ± 0.16 |
| F9 | 0.40 ± 0.03 | 0.43 ± 0.09 | 6.97 ± 0.29 | 1.07 ± 0.23 | 29 ± 0.20 |

*Average of three determinations

### 3.2. Post compression studies

The tablets were prepared and subjected for post compression evaluation tests and results are given in table 3.

**Table 3** Postcompression evaluation data of SAL-SLTs

| Batches | Weight variation mg*± SD n=20 | Friability %* ± SD n=20 | Hardness kg/cm$^2$* ± SD n=6 | % Drug content* ±SD n=3 | Wetting time sec n=3 | Water absorption ratio n=3 | Disintegration time sec n=6 |
|---|---|---|---|---|---|---|---|
| F-1 | 139.3±0.57 | 0.89±0.01 | 2.5±0.1 | 95.3±0. 5 | 36 | 1.45 | 194 |
| F-2 | 140.2±0.53 | 0.88±0.06 | 2.5±0.4 | 96.4±0.3 | 32 | 5 | 189 |
| F-3 | 139.6±0.52 | 0.91±0.08 | 2.8±0.2 | 93.2±0.4 | 29 | 3.57 | 175 |
| F-4 | 139.3±0.27 | 0.90±0.02 | 2.6±0.1 | 95.3±0.5 | 27 | 2.18 | 179 |
| F-5 | 141.1±0.57 | 0.92±0.06 | 2.8±0.4 | 96.7±0.1 | 25 | 5.7 | 161 |
| F-6 | 140.3±0.61 | 0.96±0.01 | 2.9±0.5 | 96.9±0.3 | 21 | 8.6 | 149 |
| F-7 | 139.1±0.24 | 0.93±0.05 | 2.8±0.1 | 93.2±0.2 | 45 | 6.4 | 207 |
| F-8 | 138.7±0.32 | 0.93±0.03 | 2.9±0.3 | 95.7±0.3 | 42 | 2.9 | 196 |
| F-9 | 140.3±0.22 | 0.96±0.02 | 3.0±0.4 | 94.1±0.5 | 41 | 8.1 | 185 |

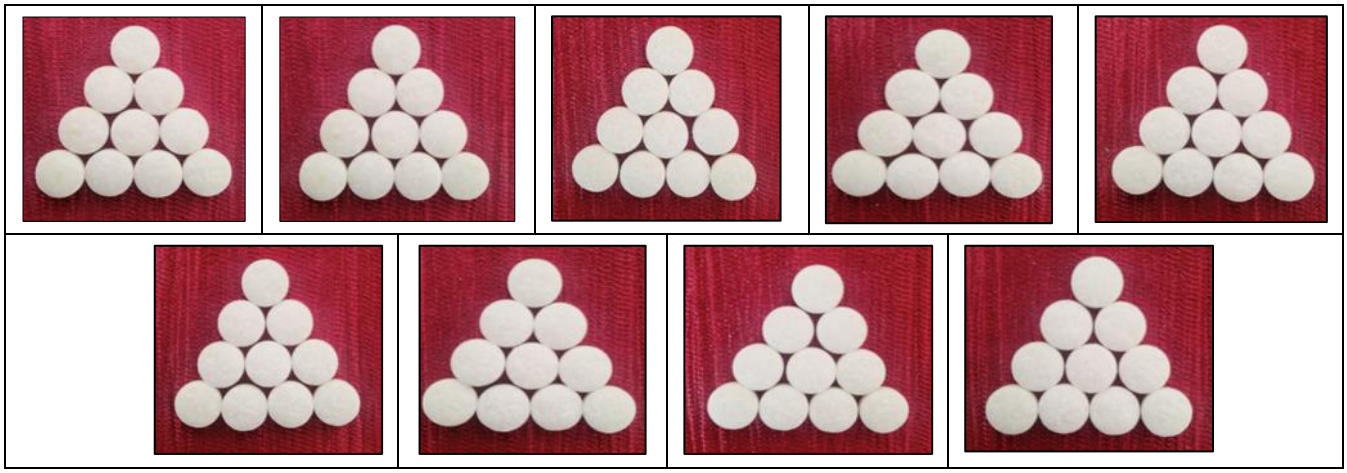

**Figure 1** Digital photographs of SAL-SLTs

## 4. Discussion

The present study was an attempt to prepare and evaluate SAL-SLTs using super disintegrating agents for the treatment of asthma and COPD by direct compression method. SAL initially was tested for the melting point as an identification test. The melting point of was found to be 158.00°C which is as per the specifications mentioned in IP. Absorption maxima for SAL when observed under UV–visible spectrophotometer were found to be at 224 nm. Calibration curve of salbutamol sulphate was obtained at concentration of 5–30 µg/ml with $R^2$ value 0.9996. Total weight of tablet was targeted for 140 mg. All formulations (F1 to F9) were found to be white in color, odorless, round flat without break-line on one side. The prepared powder blends of above batches were evaluated for precompression characteristics viz., bulk density, tapped density, Hausner's ratio, angle of repose, carr's index. These fabricated tablets were evaluated for post compression evaluation parameters viz., thickness, diameter, weight variation, drug content uniformity, hardness, friability, wetting time, water absorption ratio and *in vitro* dissolution. The results of FTIR spectra indicates that salbutamol was compatible with other excipients indicating no drug excipients interaction, and all the characteristic IR peaks related to pure drug (like tri-methyl groups, secondary amine group, or phenol groups), were appeared in the IR spectrum of the formulas F3, F6, and F9.

### 4.1. Precompression and postcompression studies

The bulk density was found to be in the range of 0.40 ±0.08 g/cm$^3$ to 0.44 ± 0.09 g/cm$^3$; tapped density was found to be in the range of 0.43 ± 0.04 to 0.54 ± 0.04 g/cm$^3$; and Hauser's value was found to be in the range of 1.04 to 1.22 indicates a powder with good flow properties. All the formulations showing that the blend of powder for formulation having good flowability. The angle of repose was found to be 26º to 29º indicates blend was free flowing and can be used for direct compression. Thickness of the prepared tablets was found to be in the range of 2.8 ±0.02 mm to 2.9 ±0.04 mm for F-1 to F-9 formulations. Diameter of the prepared tablets were found to be 8.0±0.11 to 8.2±0.06. The results were within the limits and are in accordance with Pharmacopoeial standards. The hardness of the tablets was found to be in the range of about 2.5 ±0.112 kg/cm$^2$ to 3.0 ±0.115 and friability was found to be in the range of 0.88 ±0.103 to 0.96 ±0.112 % which was below 1% indicating the sufficient mechanical integrity and strength of the prepared tablets. The hardness and friability data indicates good mechanical strength/resistance to the tablets.

The weight variation results revealed that average percentage deviation for 20 tablets was less than ±7.5%, which provide good uniformity of the tablets and were found to be within acceptable limits as per the Pharmacopoeial specifications, whereas the percentage drug content was found to be in the range of 93.2±0.4% to 96.9±0.3%. The low SD values indicate the drug content was uniform in all the formulated tablets. The disintegration time were found to be in the range of 149 to 207 sec. It was observed that the better disintegration time in the formulation F6 with CP as super disintegrant showed faster disintegration time compared with that of other formulations i.e. higher the concentration of super disintegrant used, the shorter the time required for the tablet to disintegrate. Wetting time is other important related parameters to water absorption, which needs to be assessed to give an insight into the disintegration properties of tablets. Wetting time corresponds to the time taken for the tablet to disintegrate when motionless on the tissue paper in a petridish. This method will duplicate the *in vivo* disintegration, as the tablet is kept motionless beneath the tongue. The average wetting time for all the formulations was in the range of 21 to 45 seconds. The maximum wetting time of 45 seconds and minimum wetting time of 21 seconds were shown by F7 and F6 respectively. Ratio of water absorption and time of wetting of all prepared tablets were observed to be in the prescribed limits.

### 4.2. *In-vitro* drug release study

*In vitro* drug dissolution studies were carried out for SAL-SLTs using USP XXII dissolution apparatus type II. Dissolution was carried out in phosphate buffer pH 6.8 up to 30 min. In each time interval specified amount of fluid was withdrawn and same was replaced with fresh dissolution medium to maintain the sink conditions. We noted the drug release at 5, 10, 15, 20, 25 and 30 minutes for all prepared formulations. The cumulative percentage of drug release for formulations, F1 to F9 was found to be 29.95 %, 31.10 %, 33.07 %, 30.64%, 34.05%, 38.65%, 25.67%, 26.66%, 28.14% during 5min respectively. And maximum percentage of drug release was found to be 93.74%, 94.27%, 95.45 %, 94.93 %, 95.72 %, 97.69 %, 94.01%, 94.53 %, and 95.32 % during 30 min respectively. From the above studies, it was observed that increase in concentration of super disintegrant i.e. CCS/CP/SSG, the percentage of drug release increased. Among the all formulations (F1 to F9), the best *in-vitro* drug release observed in formulation, F6 was found to be 97.69 %, as increase the concentration of CP that is due to result of rapid disintegration. During the dissolution studies, it was observed that the tablets were initially erodible over period of time. The *in-vitro* drug release data of all SAL-SLTs were subjected to goodness of fit test by linear regression analysis according to Zero order equation, I$^{st}$ order equation, Higuchi's equation and Korsmeyer-Peppas equation to ascertain the mechanism of drug release. Among the regression correlation co-efficient ($R^2$) values of I$^{st}$ order equation was found to be higher. Hence the drug release followed I$^{st}$ order release kinetics with diffusion mechanism. Finally, dissolution data for all the formulations with different polymers was fitted into various kinetic models for depicting the mechanism of drug release from the sublingual tablets. In all the formulations the best fit model was found to be first order with 'r' value 0.9956, 0.9966, 0.9961, 0.9957, 0.9957, 0.9935, 0.9936, 0.9932 and 0.9922 for F1 to F9 formulations respectively. In all the formulations exponential 'n' value was found to be less than 0.5 indicating the drug release follows fickian diffusion mechanism.

## 5. Conclusion

From the above results it can be concluded that *in vitro* dissolution studies suggest a direct relationship of concentration of super disintegrant with drug release irrespective of diluents used in the studies. The dissolution data was fitted with various kinetic models using dissolution software PCP DissoV.3. *In vitro* drug release indicated that the drug release was most extreme in formulation F6 (97.69 %) at 30 min. Incorporation of super disintegrants yielded great outcome in terms of percentage of drug release. These findings suggest that salbutamol sulphate sublingual tablets can be considered as potential drug delivery system for the treatment of asthma and COPD.

## Compliance with ethical standards

*Acknowledgments*

The authors are thankful to Sain medicaments Pvt ltd, Hyderabad for providing the API salbutamol sulphate and to the principal and management of V. L. College of pharmacy for providing the facilities to carry out this research work.

*Disclosure of conflict of interest*

There are no conflicts of interest.

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