ORIGINAL ARTICLE

Design, development, and evaluation of terbutaline sulfate sublingual tablets

Narendra Yadav, Mangal Singh Panwar[1]

Department of Pharmaceutics, B. R. Nahata College of Pharmacy, [1]Department of Pharmaceutical Chemistry, Mandsaur Institute of Pharmacy, Mandsaur, Madhya Pradesh, India

Terbutaline sulphate is a selective B2 bronchodilator which is used in the treatment of asthma. Conventional Terbutaline tablets available in the market are not suitable where quick onset of action is required. Terbutaline sulphate sublingual tablets were prepared by using mannitol, microcrystalline cellulose pH102 (F1) and lactose monohydrate, microcrystalline cellulose pH102 (F4) as filler and its combination in different ratio, Crospovidone as superdisintegrant and sodium lauryl Sulphate as permeability enhancers by drug dispersion direct compression method. The formulation F1 found the 93.51% of % drug permeability, 8 seconds disintegration time and 96.95% drug release within one minute. The formulation F4 also found the 98.25% of drug permeability, 13 seconds disintegration time and 90.31% drug release within one minute. It was concluded that the sublingual tablet of Terbutaline sulphate can be formulated for sublingual absorption of drug in emergency treatment of asthma by Mannitol and Microcrystalline cellulose pH 102 in combination (75% and 25% respectively) or lactose monohydrate and Microcrystalline cellulose pH 102 in combination (75% and 25% respectively) as filler, Crospovidone as superdisintegrant, and Sodium Lauryl sulphate as permeability enhancer by direct compression drug dispersion method.

Key words: *Dispersion method, drug permeability, sublingual, superdisintegrant*

INTRODUCTION

Sublingual, literally "under the tongue," from Latin, refers to a pharmacological route of administration in which certain drugs are entered directly into the bloodstream via absorption under the tongue. Many pharmaceuticals are prepared for sublingual administration. These commonly include cardiovascular drugs, steroids, barbiturates, some enzymes, and increasingly frequently, certain vitamins and minerals.[1] The sublingual route offers an attractive alternative for systemic drug delivery of drugs because of better patient compliance, ease of dosage form removal in emergencies, robustness, and good accessibility. Within the oral mucosal cavity, the sublingual region offers an attractive route of administration for systemic drug delivery. The mucosa has a rich blood supply, and it is relatively permeable.[2] It is the objective of this article to review sublingual drug delivery by discussing the structure and environment of the oral mucosa and the experimental methods used in assessing sublingual drug permeation/absorption. Sublingual dosage forms will also be reviewed with an emphasis on bioadhesive polymeric based delivery systems.[3]

The principle behind the sublingual administration is fairly simple. When a chemical comes in contact with the mucous membrane, or buccal mucosa, it diffuses into the epithelium beneath the tongue. This region contains a high density of blood vessels, and, as a result, via diffusion, the substance quickly enters the venous circulation, which returns to the heart and then travels to the systemic arterial circulation. In contrast, substances absorbed by the bowel are subject to "first pass metabolism" in the liver before they are distributed to the rest of the body.[4-6]

In theory, sublingual routes of administration have certain advantages over simple oral administration. This route is often faster, and entering a drug into one's body sublingually ensures that the substance will only come in contact with the enzymes in saliva

Address for correspondence:
Prof. Narendra Yadav,
Department of Pharmaceutics, B. R. Nahata College of Pharmacy,
Mhow Neemuch Road, Mandsaur - 458 001, Madhya Pradesh, India.
E-mail: nandu1105@rediffmail.com

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.160311

prior to entry into the bloodstream. Drugs otherwise orally administered must instead survive the incredibly hostile environment of the gastrointestinal (GI) tract.[7,8] This may mean a much greater percentage of the original substance is degraded either by the myriad of enzymes in the GI tract, like monoamine oxidase or the strong acids it contains. In addition, after GI absorption, the drug is sent to the liver where the drug may be extensively metabolized; this is known as the first pass effect of drug metabolism.[9,10] Due to the degradative qualities of the stomach and intestine, or the solubility of the GI tract, certain substances, such as salvinorin A may only be administered orally via the sublingual route. Because of its size and relative fragility, salvinorin A cannot pass the GI tract intact and must instead be absorbed across a mucous membrane.[11] The sublingual glands are salivary glands in the mouth. They lie anterior to the submandibular gland under the tongue, beneath the mucous membrane of the floor of the mouth. They are drained by 8–20 excretory ducts. The largest duct, the sublingual duct (of Bartholin) joins the submandibular duct to drain through the sublingual carbuncle.[12,13] The oral cavity (i.e. sublingual, buccal, and local drug delivery) selecting one over another is mainly based on anatomical and permeability differences that exist among the various oral mucosal sites. The sublingual mucosa is relatively permeable, giving rapid as stated above in section I, there are three different categories of drug delivery within absorption and acceptable bioavailability of many drugs, and is convenient, accessible, and generally well accepted.[14,15]

EXPERIMENTAL

Formulation of sublingual tablet of terbutaline sulfate

Formulation of sublingual tablet of terbutaline sulfate was done as follows:

Preparation of dummy tablets was done by using different diluents such as lactose monohydrate, mannitol, microcrystalline cellulose, and its combination in the different ratio for selecting the filler in the current formulation. Then the tablets were prepared by using superdisintegrants, permeability enhancers, and other excipients such as lubricants, glidants, sweetener, etc., to select the best formulation of sublingual tablet and finally the tablets were prepared by different methods such as direct compression (DC), wet granulation, and DC drug dispersion to select the appropriate method for the formulation.

Preparation of dummy tablets

Dummy tablets were prepared by using different diluents such as lactose monohydrate, mannitol, microcrystalline cellulose, and its combination in different ratio. This step was done only to study the effect of diluents on tablet characteristics and for selection of diluent for further formulations of tablets [Table 1].

From this step, it was concluded that the mannitol, microcrystalline cellulose pH 102, and lactose monohydrate in ratios of 75% and 25% are suitable for further preparation of sublingual tablet.

Preparation of tablets

The tablets were prepared by using superdisintegrant, permeability enhancers, lubricants, glidants to formulate the sublingual tablets containing terbutaline sulfate [Table 2].

Formulation of tablet by different preparation methods

In this step, the tablet was prepared by different process. This step was done to see the effect of preparation method and to select the preparation method for further formulation of sublingual tablets. Different methods used for formulating the sublingual tablets were following:

- DC
- Wet granulation
- DC drug dispersion.

Direct compression

The DC of tablet performed into three steps:

- Dry mixing
- Lubrication
- Compression.

Dry mixing

The diluent (mannitol DC/microcrystalline cellulose pH 102/ lactose monohydrate) pass through sieve no. 30 and crospovidone were weighed and passed through sieve no. 40 and mixed.

Lubrication

Terbutaline sulfate, aerosil, magnesium stearate, aspartame, sodium lauryl sulfate (SLS), and purified talc were bag blended. Blend was passed through mesh 60 stainless steel (ss) screen fitted and then above dried granules were mixed with the blend in a suitable blender.

Compression

Lubricated granules compressed into a tablet by using single rotary tablet Punching machine (CADMAC), 12 stations. With D tooling punch sets.

Wet granulation

The Wet granulation process performed into three steps.

- Dry mixing and granulation
- Lubrication of granules
- Compression of lubricated granules.

Dry mixing and granulation

Weighed the diluent (mannitol DC/microcrystalline cellulose pH 102/lactose monohydrate) and crospovidone were blended and passed through sieve no. 40. Then the starch paste was added on the blend while the dry blend was being mixed.

Table 1: Formulation of dummy tablets

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Mannitol I.P	97	-	-	72.25	24.75	72.25	24.75	-	-
Microcrystalline cellulose (pH 102) I.P	-	97	-	24.75	72.25	-	-	72.25	24.75
Lactose monohydrate I.P	-	-	97	-	-	24.75	72.25	24.75	72.25
Purified talc I.P	1	1	1	1	1	1	1	1	1
Magnesium stearate I.P	1	1	1	1	1	1	1	1	1
Colloidal silicon dioxide I.P	1	1	1	1	1	1	1	1	1

All quantity in mg/tablet, compression weight of tablet - 100 mg/tablet

Table 2: Formulation of terbutaline sulfate tablets

Ingredients	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Terbutaline sulfate I.P	3	3	3	3	3	3	3	3	3
Mannitol I.P	65.1	21.7	-	-	65.1	21.7	80	-	-
MCC (pH 102) I.P	21.7	65.1	65.1	21.7	-	-	-	-	80
Lactose monohydrate I.P	-	-	21.7	65.1	21.7	65.1	-	80	-
Maize starch B.P	-	-	-	-	-	-	6.83	6.83	6.83
Crospovidone B.P	5	5	5	5	5	5	5	5	5
Sodium lauryl sulfate B.P	1	1	1	1	1	1	1	1	1
Purified talc I.P.	1	1	1	1	1	1	1	1	1
Magnesium stearate I.P	1	1	1	1	1	1	1	1	1
Colloidal silicon dioxide I.P	1	1	1	1	1	1	1	1	1
Aspartame I.P	1	1	1	1	1	1	1	1	1
Flavor	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2

All quantity in mg/tablet, compression weight of tablet - 100 mg/tablet. MCC: Microcrystalline cellulose

Wet mass was passed through mesh 8 ss screen fitted of the sifter and semi-dried. Semi-dried granules were passed through sieve no. 16 and sieve no. 30, dried at 60°C in tray dryer until the loss on drying (LOD) was observed about 0.5% (On insulin receptor [IR] at 105°C for 5 min).

Lubrication of granules

Terbutaline sulfate, aerosil, magnesium stearate, aspartame, SLS, and purified talc were bag blended. Blend was passed through mesh 60 ss screen fitted and then above dried granules were mixed with the blend in a suitable blender.

Compression of lubricated granules

The lubricated granules were compressed into a tablet by using single rotary tablet Punching machine, 12 stations. With D tooling punch sets.

Direct compression drug dispersion

The DC drug dispersion process performed into four steps:

- Drug dispersion
- Dry mixing
- Lubrication of dry granules
- Compression of lubricated granules.

Drug dispersion

Terbutaline sulfate was dissolved in distilled water and dispersed onto the diluent (mannitol DC/microcrystalline cellulose pH 102/lactose monohydrate) Wet mass was passed through mesh 8 ss screen fitted of the sifter and semi-dried. Semi-dried granules were passed through sieve no. 16 pass through sieve no. 30, dried in tray dryer until the LOD was observed about 0.5% (on IR at 105°C for 5 min).

Dry mixing

The other diluent (mannitol DC/microcrystalline cellulose pH 102/lactose monohydrate), crospovidone passed through mesh 40 ss screen and blended. The passed blend was mixed with above formed granules.

Lubrication of granules

Magnesium stearate, purified talc, aspartame, SLS, and aerosil were bag blended. Blend was passed through mesh 60 ss screen fitted and then above dried granules were mixed with the blend in a suitable blender.

Compression of lubricated granules

The lubricated granules were compressed into a tablet by using single rotary tablet Punching machine, 12 stations. With D tooling punch sets.

From the above study, it was concluded that the DC drug dispersion method provide good tablets characteristics. Therefore, for the uniform distribution of the drug this method was selected for the further formulation of sublingual tablets.

RESULTS AND DISCUSSION

Standard calibration curve of terbutaline sulfate 100 mg of terbutaline sulfate was dissolved in 100 ml of phosphate buffer

pH 6.8. From the stock solution, 10 ml was further diluted to 100 ml with phosphate buffer pH 6.8. Then from this solution, aliquots of 1–10 ml were pipette out and made up to 10 ml with phosphate buffer pH 6.8. The absorbance of the above solution was measured at 286 nm by a ultraviolet spectrophotometer (CADMAC). The standard graph was plotted.

Table 3 and Figures 1 and 2 shows the absorbance readings of terbutaline sulfate between 10 and 100 mcg/ml in phosphate buffer pH 6.8

Standard curve of terbutaline sulfate

Standard curve of terbutaline sulfate was plotted by taking absorbance on X-axis and concentration in mcg/ml on Y-axis. The plotted graph is shown in Figure 2.

Evaluation of granules

Angle of repose

The angles of repose of all formulated batches obtained are shown in Table 4. This implies the fair free flowing nature of granules. These values were found to be satisfactory to give a good flow of granules.

Table 3: Standard calibration curve of terbutaline sulfate

Concentration (mcg/mL)	Absorbance
10	0.0673
20	0.1260
30	0.1933
40	0.2678
50	0.3273
60	0.3952
70	0.4581
80	0.5139
90	0.6134
100	0.6733

Hausner ratio

The values of Hausner ratio obtained are shown in Tables 4 and 5, indicating that the granules had good flowability and compressibility.

Bulk density and tapped density

The values of bulk density and tapped density obtained are shown in Tables 4 and 5, indicating that the granules had good compressibility. Thus, the granules blends were found within specification.

Evaluation of tablets

Tablet thickness

Five tablets of each formulation were evaluated and mean thickness values obtained are shown in Table 6.

The value indicates that, die fill was uniform, and compression force was constant.

Hardness

Five tablets of each formulation were evaluated and mean hardness values are shown in Table 6. The value reveals that the tablets are having good mechanical strength.

Friability

Friability values for each formulation are recorded in Table 6. These values are within the acceptable limit, implies good compactness, and strength of each formulation. This also indicates that wet granulation method is an acceptable technique for formulating rapidly disintegrating sublingual tablets.

Table 4: Sublingual tablets of terbutaline sulfate with superdisintegrants, permeability enhancers, sweeteners, and other excipients evaluation parameters of granules of terbutaline sulfate

Parameters	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Loss on drying, %	0.6	1.2	1.2	0.4	0.6	0.6	1.25	1	0.8
Angle of repose, degree	14°C 92′	17°C 19′	16°C 38′	16°C 62′	16°C 38	15°C 31′	15°C 87′	16°C 12′	16°C 21′
Bulk density, g/cm^3	0.5263	0.4347	0.4166	0.5263	0.625	0.5555	0.5555	0.5555	0.4243
Tapped density, g/cm^3	0.625	0.5263	0.5263	0.625	0.7142	0.625	0.625	0.625	0.5260
Percentage of compressibility	15.79	17.40	20.84	15.79	12.50	11.12	11.12	11.12	19.33
Hausner ratio	1.18	1.21	1.26	1.18	1.14	1.12	1.12	1.12	1.23

Table 5: Dummy tablets with different diluents

Parameters	Fd_1	Fd_2	Fd_3	Fd_4	Fd_5	Fd_6	Fd_7	Fd_8	Fd_9
Angle of repose, degrees	24.21	23.35	21.6	23.85	22.68	23.14	22.88	21.94	22.59
Bulk density, g/cm^3	0.62	0.55	0.42	0.53	0.52	0.52	0.52	0.56	0.52
Tapped density, g/cm^3	0.71	0.66	0.55	0.62	0.62	0.66	0.63	0.66	0.66
Percentage of compressibility	12.46	16.66	23.6	14.51	16.12	21.21	17.46	15.15	21.21
Hausner ratio	1.14	1.2	1.30	1.17	1.19	1.26	1.21	1.17	1.26
Hardness, kg/cm^2	1.5	2.4	5	1.5	1.5	2.1	2.2	3	3
Thickness, mm	2.86	2.83	2.80	2.83	2.84	2.84	2.82	2.81	2.80
Disintegration time, min	1	2.5	1.45	1.55	2.23	2.53	2.37	2.11	2.03
Percentage of friability	8	0.24	0.12	6	5	2.9	2.5	0.18	0.15
Weight variations, average weight mg	100.23	100.4	99.8	101.5	101.1	100.8	100.1	99.52	99.12

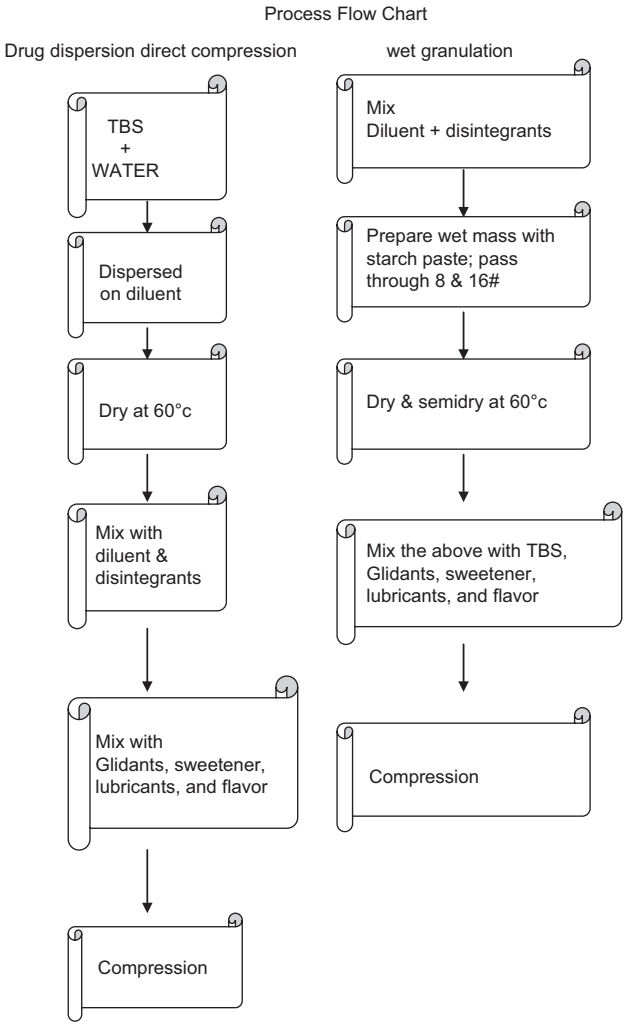

Figure 1: Process flow chart

Average weight

Twenty tablets of each formulation were evaluated. The mean values of each formulation are recorded in Table 6. The values obtained dictates that all the tablet of different formulations falls within the USP specifications.

The weight variation of all tablets was satisfactory due to good granule flowability; desired packing characteristics; and uniform dies fill of all the formulations. This is supported by the acceptable flow properties of granules obtained.

Content uniformity of active ingredient

The content uniformity was calculated on all the formulations of sublingual tablets. Table 6 shows the results of the drug content uniformity in each formulation with standard deviation values.

These values are found satisfactory, which ensures dosage uniformity and meets with requirements of USP in which ± 10% deviation is acceptable.

Disintegration time

The disintegration time for each formulation was calculated, and the study was carried out in triplicate. Table 6 shows the results of the disintegration time of each formulation. The crospovidone, 5% of total weight of the tablet, produce rapid disintegration. These values show that the tablets disintegrate rapidly.

Wetting time

The wetting time was calculated in triplicate, and Table 6 shows the results of the wetting time and water absorption of each formulation.

Table 6: Evaluation parameters of sublingual tablets of terbutaline sulfate

Parameters	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
Hardness, kg/cm^2	2.5	3	3	3	2.5	3	3.5	4	3
Thickness, mm	2.64	2.69	2.78	2.82	2.54	2.58	2.82	2.74	2.78
Weight variation, average, weight mg	100.2	100.1	99.75	100.85	100.35	101.5	101.25	102.85	101.28
Percentage of friability	0.02	0.007	0.004	0.01	0.25	0.037	0.072	0.095	0.09
Disintegration time, (s)	8	8	7	13	15	14	18	35	15
Wetting time, (s)	7	6	6	9	10	12	14	33	10
Percentage of drug permeability	93.51	49.45	45.63	98.25	55.23	43.72	35.05	43.12	46.40
Percentage of drug release, in 1-min	96.95	81.47	82.57	90.31	95.84	81.10	94.00	90.31	85.52
Percentage of drug content ±SD	93.73±0.51	93.79±0.56	98.96±1.32	95.82±0.21	93.90±0.45	93.75±0.51	95.83±0.22	97.44±0.79	93.80±0.49
Content uniformity, % ±SD	95.29±5.2	91.85±1.64	93.73±0.98	97.89±5.1	91.07±1.92	87.9±3.29	106.3±3.46	96.23±0.09	95.18±0.47

SD: Standard deviation

Percentage drug permeability

The drug permeability studies of each formulation were carried out in triplicate, and Table 6 shows the results of the percentage of drug permeability of each formulation. The drug permeability study showed that the formulation F_1 contained SLS 1%, and formulation F_4 contained SLS 1% of total weight of the tablet, has good sublingual mucosal permeability 93.51% and 98.25%, respectively. The formulations F_2, F_3, F_5, F_6, F_7, F_8, and F_9 also shown good permeability, but they did not produce drug permeability to desired level. The formulation F_4 had shown the best mucosal permeability due to SLS in the concentration 1% of total weight of the tablet. Therefore formulations F_1 and F_4 were selected as final formulations.

In vitro drug release study

The formulations were subjected to *in vitro* dissolution study using USP dissolution apparatus. The percentage of drug release was calculated for different formulation at different time intervals. The results obtained in *in vitro* dissolution studies for different formulations are recorded in Tables 6 and 7 for formulations F_1–F_9. The data obtained in the *in vitro* dissolution study are grouped as follows: Percentage drug release versus time in minutes. *In vitro* dissolution study shows that the formulation F1 contained SLS 1% of total weight of tablet, provide 96.95% drug release within 1-min and the formulation F_4 contained SLS 1% provide 90.31% drug release within 1-min The formulations F_2, F_3, F_5, F_6, F_7, F_8, and F_9 produce < 90% drug release within 1-min, formulations F_1 and F_4 were selected as final formulations.

Stability studies of optimized batch F_1 and F_4

It is the responsibility of the manufacturers to see that the medicine reaches the consumer in an active form. Hence, the stability of pharmaceuticals is an important criterion. Stability of medicinal products may be defined as the capability of a particular formulation in a specific container to remain within its physical, chemical, microbial, therapeutic, and toxicological specification, that is, stability of drug is its ability to resists deterioration. Ninety percentage of labeled potency is generally recognized as the minimum acceptable potency level. Deterioration of the drug may take several forms arising from changes in physical, chemical, and microbiological properties. The changes may affect the therapeutic value of preparation or increase its toxicity [Tables 8-11].

Accelerated stability testing

Since the period of stability testing can be as long as 2 years, it is time consuming and expensive. Therefore, it is essential to devise a method that will help the rapid prediction of the long-term stability of the drug. The accelerated stability testing is defined as the validated method by which the product stability may be predicted by storage of the product under conditions that accelerate the change in defined and predictable manner.

The stability studies of formulated tablets were carried out at 40°C, relative humidity 75%, and at room temperature for 1-month. The effects of temperature and time on the physical characteristics of the tablet were evaluated for assessing the stability of the prepared formulations. The stability studies were

Table 7: *In vitro* dissolution profiles of F_1-F_9 stored at room temperature

Time in min	F_1	F_2	F_3	F_4	F_5	F_6	F_7	F_8	F_9
1	96.95	81.47	82.57	94.31	85.84	81.10	94.00	90.31	85.52
2	70.73	65.23	68.44	79.72	69.90	64.00	72.88	63.63	65.20
3	64.62	58.11	60.38	72.39	61.12	56.25	59.90	52.25	56.54
5	61.61	42.66	42.81	57.60	48.5	41.55	46.66	40.5	45.36

Table 8: Stability parameters of formulations B_1 and B_4 stored at room temperature

Parameters	B_1			D_4		
	Controlled	After 1-month	After 3 months	Controlled	After 1-month	After 3 months
Drug content (%)	93.73	93.90	97.49	95.82	93.50	96.16
Disintegration time, (s)	8	8	8	13	13	12
Wetting time, (s)	7	8	7	10	9	9
Percentage of drug permeability	93.51	94.76	92.36	98.2	91.16	89.09

Table 9: Stability parameters of formulations B_1 and B_4 stored at temperature (40°C and RH 75%)

Parameters	B_1			B_4		
	Controlled	After 1-month	After 3 months	Controlled	After 1-month	After 3 months
Drug content (%)	93.73	93.22	96.08	95.82	94.37	98.55
Disintegration time, (s)	8	7	7	13	13	13
Wetting time, (s)	7	6	6	10	8	8
Percentage of drug permeability	93.51	93.02	91.05	98.2	95.74	92.69

RH: Relative humidity

Table 10: *In vitro* dissolution profile of formulations F_1 and F_4 stored at room temperature

Time in min	Percentage of drug release F_1			Percentage of drug release F_4		
	Controlled	After 1-month	After 3 months	Controlled	After 1-month	After 3 months
1	96.95	96.58	95.47	94.31	93.26	89.20
2	70.73	71.51	68.56	79.72	78.52	81.83
3	64.62	65.98	62.29	72.39	73.36	73.35
5	61.61	62.30	57.50	57.60	53.82	56.39

Table 11: *In vitro* dissolution profile of formulations F_1 and F_4 stored at temperature (40°C and RH 75%)

Time in min	Percentage of drug release F_1			Percentage of drug release F_4		
	Controlled	After 1-month	After 3 months	Controlled	After 1-month	After 3 months
1	96.95	93.22	91.78	94.31	94.37	92.15
2	70.73	81.47	78.14	79.72	88.84	87.72
3	64.62	79.99	75.19	72.39	79.62	77.77
5	61.61	74.09	71.87	57.60	69.67	66.35

RH: Relative humidity

carried out when the room temperature was 20°C–25°C. The different parameters that were studied are *in vitro* disintegration time, wetting time, drug content, the percentage of drug permeability study, and *in vitro* dissolution rate [Figure 4].

Comparison with marketed products

The promising formulations F_1 and F_4 obtained in evaluation study were compared with marketed formulations. The evaluation parameters tested and compared. The Formulations F_1 and F_4 were compared with marketed formulations were justified as B_1 and B_2. The formulations F_1 and F_4 were compared mainly for drug permeability and percentage of drug release. The F_1 produces 93.51% mucosal permeability in 5 min, disintegrates in 20 s, and 96.95% drug release within 1-min. Formulation F_4 produces 98.25% mucosal permeability in 5 min, disintegrates in 13 s, and 90.31% drug release within 1-min.

The marketed formulation B_1 produces 15% mucosal permeability after 1-min and 100% release in 3 min, the B_2 produces 10% mucosal permeability in 5 min and 100% drug release in 5 min. The above study has shown that the drug permeability and *in vitro* dissolution profile of formulations F_1 and F_4 were found to be comparable with marketed products and it is shown that the formulations F_1 and F_4 are better for sublingual administration than B_1 and B_2 [Tables 12 and 13, Figure 3].

Table 12: Comparison of final batches F_1 and F_4 with marketed conventional tablets B_1 and B_2

Parameters	F_1	F_4	B_1	B_2
Disintegration time, (s)	8	13	2 min 30 s	3 min 50 s
Percentage of drug permeability (in 5 min)	93.51	98.25	24.31	22.79
Percentage of drug release in 1-min	96.95	94.31	18.79	16.60

Table 13: Percentage drug release from formulations F_1, F_4, B_1, and B_2 in phosphate buffer pH 6.8

Time in min	Percentage of drug release of F_1	Percentage of drug release of F_4	Percentage of drug release of B_1	Percentage of drug release of B_2
1	95.47	89.20	18.79	16.60
2	68.56	81.83	27.79	24.06
3	62.29	73.35	34.23	30.84
5	57.50	56.39	38.25	34.90

SUMMARY AND CONCLUSIONS

In the present work, sublingual tablets were prepared by selecting diluents, superdisintegrant, preparation method and permeation enhancers and evaluated for disintegration time, hardness, friability, wetting time, percentage of permeability, *in vitro* dissolution time, content uniformity, and drug content.

Formulation of the sublingual tablet was done as follows: Preparation of dummy tablets was done by using different diluents such as Lactose Monohydrate, Mannitol, Microcrystalline Cellulose, and its combination in different ratio. Then the tablets were prepared by using superdisintegrants, permeability enhancers, and other excipients such as lubricants, glidants, sweetener, etc., to select the best formulation of sublingual tablet. Then the tablets were prepared by different method by DC, wet granulation, and DC drug dispersion method.

The dummy tablets were prepared by using different filler and its combination in different concentrations. The total nine dummy tablets were prepared and evaluated for hardness, disintegration time, weight variation. All the formulation shows hardness and weight variation within the limit.

The rapid disintegrating sublingual tablets were prepared by different preparation methods such as DC, wet granulation,

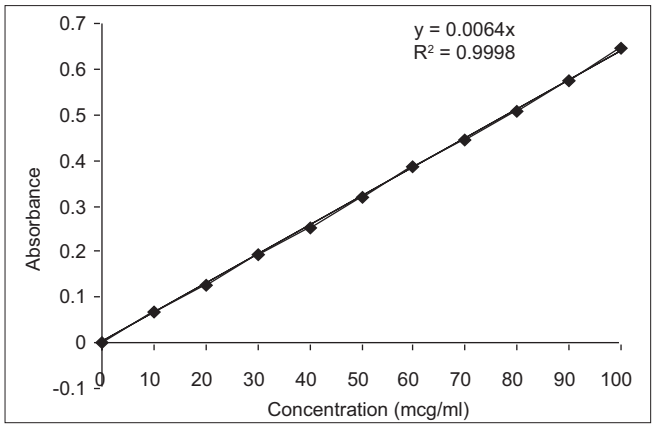

Figure 2: Standard curve of terbutaline sulfate

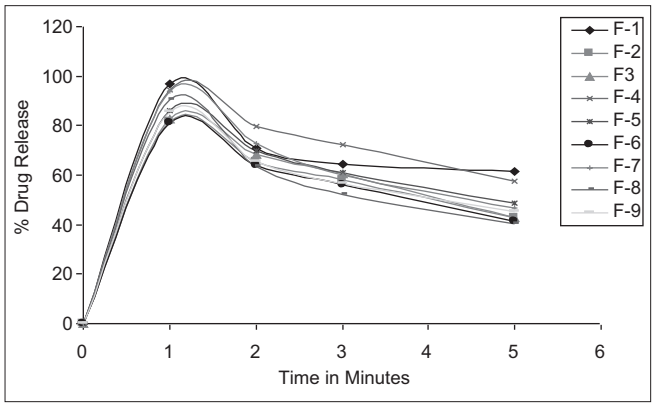

Figure 3: *In vitro* dissolution profiles of F1–F9

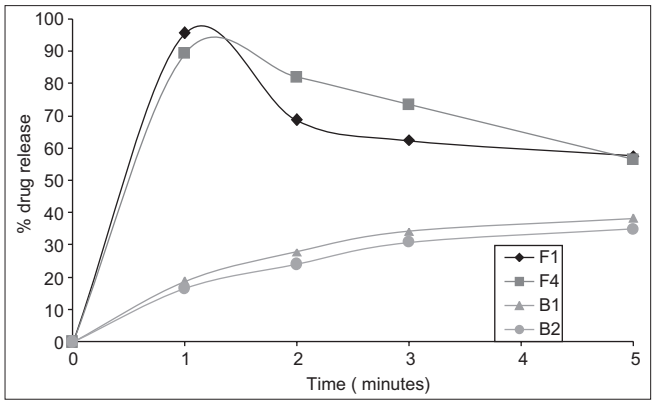

Figure 4: A comparison of percentage drug release of formulations F1 and F4 with marketed tablets B1 (bricanyl) and B2 (brethine)

DC drug dispersion, and wet granulation drug dispersion. The prepared tablets were evaluated for content uniformity and physical parameters. The DC drug dispersion found the content uniformity within the limit and tablets prepared by other methods were not passed the uniformity content, in this formulation content, uniformity is very important because of terbutaline is very potent drug and its dose is very small, so the DC drug dispersion method was selected for final formulations.

The results of evaluation parameters can be summarized as follows:

- Results of the evaluation of granules exhibited good flowability and compressibility
- Uniformity in tablet dimensions implies that die fill was uniform and compression force was constant
- Hardness values reveal that tablets are having good mechanical strength and handling characteristics
- Friability values dictate good compactness of the formulations
- The weight variations of all formulated tablets were satisfactory, attributed by the acceptable flow properties of granules
- Content uniformity of active ingredient of all the formulation is within the acceptable limit and ensures dosage uniformity
- Promising formulations were compared with marketed formulations, which show that formulation exhibits drug release pattern, which is greater when compared with the marketed formulation.

Finally, rapidly disintegration tablets were prepared by using mannitol, microcrystalline cellulose pH 102 (F_1) and lactose monohydrate, microcrystalline cellulose pH 102 (F_4) as filler, crospovidone as superdisintegrant, and SLS as permeability enhancers. The total nine formulations were prepared and evaluated for hardness, friability and weight variation, content uniformity, wetting time, disintegration time, the percentage of permeability, and *in vitro* drug release. All the formulations found the evaluation results within the limit. The formulation F_1 found 93.51% of the percentage of drug permeability, 8 s disintegration time, and 96.95% drug release within 1-min. The formulation F_4 also found 98.25% of drug permeability, 13 s disintegration time, and 90.31% drug release within 1-min.

Best formulations F_1 and F_4 were compared with the conventional marketed formulations of B_1 (Bricanyl) and B_2 (Brithine) for disintegration time, the percentage of drug permeability, and *in vitro* drug release. The disintegration time, percentage of drug permeability, and percentage of drug release for B_1 was 2 min 30 s, 24.31%, and 18.79%, respectively, and that of B_2 was 3 min 50 s, 22.79%, and 16.60%, respectively.

The stability studies were performed for formulations F_1 and F_4 as per ICH guidelines for its hardness, *in vitro* disintegration time, wetting time, the percentage of drug permeability, and *in vitro* drug release pattern. The formulation showed no significant variations for the above-mentioned parameters and it was stable for the specified time period.

It was concluded that the sublingual tablet of terbutaline sulfate can be formulated for sublingual absorption of drug in emergency treatment of asthma by mannitol and microcrystalline cellulose pH 102 in combination (75% and 25%, respectively) or lactose monohydrate and microcrystalline cellulose pH 102 in combination (75% and 25%, respectively) as filler, crospovidone as superdisintegrant,

DC drug dispersion method, and SLS as permeability enhancer which enhance the sublingual permeability of drug.

Futurology

- To carry out the bioavailability studies for the formulated products
- To perform the clinical trial for making the exercise commercially viable.

REFERENCES

1. Sublingual-Wikipedia, the Free Encyclopedia. Available from: http://www.Wikipedia.com.
2. Birudaraj R, Mahalingam R, Li X, Jasti BR. Pharmacology of bronchial asthma by Vincent Lagente and Elisabeth Boichot. Adv Buccal Drug Deliv 2005;22:295-330.
3. Aungst BJ, Rogers NJ, Shefter E. Comparison of nasal, rectal, buccal, sublingual and intramuscular insulin efficacy and the effects of a bile salt absorption promoter. J Pharmacol Exp Ther 1988;244:23-7.
4. Aungst BJ, Rogers NJ. Site dependence of absorption-promoting actions of laureth-9, Na salicylate, Na2EDTA, and aprotinin on rectal, nasal, and buccal insulin delivery. Pharm Res 1988;5:305-8.
5. Lee WE. Permeation enhancers for the nasal delivery of protein and peptides therapeutics. Bio Pharm 1990;3:22-5.
6. Tengamnuay P, Mitra AK. Bile salt-fatty acid mixed micelles as nasal absorption promoters of peptides. I. Effects of ionic strength, adjuvant composition, and lipid structure on the nasal absorption of [D-Arg2] kyotorphin. Pharm Res 1990;7:127-33.
7. Shao Z, Mitra AK. Nasal membrane and intracellular protein and enzyme release by bile salts and bile salt-fatty acid mixed micelles: Correlation with facilitated drug transport. Pharm Res 1992;9:1184-9.
8. Sayani AP, Chien YW. Systemic delivery of peptides and proteins across absorptive mucosae. Crit Rev Ther Drug Carrier Syst 1996;13:85-184.
9. Rathbone MJ, Hadgraft J. Absorption of drugs from the human oral cavity. Int J Pharm 1991;74:9-24.
10. De Cries ME, Bode HE. Developments in buccal delivery. Crit Rev Ther Drug Carrier Syst 1991;8:271-303.
11. Squire CA. The permeability of oral mucosa. Crit Rev Ther Oral Biol Med 1991;2:13-32.
12. Gandhi RE, Robinson JR. Bioadhesion in drug delivery. Indian J Pharm Sci 1988;50:145-52.
13. Harris D, Robinson JR. Drug delivery via the mucous membranes of the oral cavity, reproduced with permission of the American pharmaceutical association. J Pharm Sci 1992;81:1-10.
14. Sublingual Absorption by Leilani Lei, Magazine. 1999-2002, Issue 13. Available from: http://www.pharmpedia.com.
15. Sweetman SC. Martindale the Complete Drug Reference. 34th ed.: United States: Pharmaceutical Press; 2005. p. 797-8.

How to cite this article: Yadav N, Panwar MS. Design, development, and evaluation of terbutaline sulfate sublingual tablets. Asian J Pharm 2015;9:162-70.

Source of Support: Nil. **Conflict of Interest:** None declared.