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FORMULATION AND EVALUATION OF SELEXIPAG SUBLINGUAL TABLETS

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ABSTRACT

Selexipag is a selective prostacyclin (IP, also called PGI2) receptor agonist. It is used in treatment of Pulmonary Arterial Hypertension. Selexipag Bioavailability is approximately 49%. After oral administration, maximum concentrations of Selexipag and its metabolite were observed to be reached at 1-3 and 3-4 hours, respectively. Absorption was impaired in the presence of food, resulting in delayed time to maximum concentration. In the present study, an attempt was made to improve bioavailability of Selexipag and formulate Selexipag sublingual tablets hence avoid first-pass metabolism and increase Bioavailability. To Improve Bioavailability of Selexipag, sublingual tablets were prepared. Various Superdisintegrants like Croscarmellose Sodium and Crospovidone were used. The tablet with mentioned excipients were evaluated for different parameter amongst them Mannitol and Microcrystalline Cellulose (MCC) in 60:40, 70:30 and 80:20 (Mannitol: MCC) three ratios were optimized for further formulation of sublingual tablets. The prepared tablets were evaluated for various parameters like Thickness, Hardness, Friability, Weight variation, Disintegration time, wetting time, % *In vitro* Drug Release. The stability study was carried out as per ICH guideline to meet the desirable characteristics. In a nut shell, Selexipag sublingual tablets were successfully formulated.

Keywords: Selexipag, Sublingual tablet, Croscarmellose Sodium, Crospovidone, Mannitol and Microcrystalline Cellulose

INTRODUCTION

The systemic drug delivery provide immediate onset of pharmacological effects through the sublingual route. Dysphasia (Difficulty in swallowing) is common problem of all age groups or on reduced liquid intake have difficulties in swallowing the solid dosage forms. Sublingual administration of the drug means placement of drug i.e. dosage form under the tongue & drug reaches directly into the systemic circulation [**1, 2**]. It is estimated that 25% of the population find difficulty in swallowing conventional solid dosage forms like tablets and capsules and therefore do not take their medication as prescribed by the physician resulting in high incidence of non-compliance and ineffective therapy **[3, 4, 5]**. Mainly this difficulty is experienced in particular by pediatrics and geriatric patients. It also applies to people who are bedridden and to those active working patient who are busy travelling, especially those who have no access to water Sublingual drug delivery is alternative approach to the enteral drug delivery. It avoids first pass metabolism in liver and gastric acid hydrolysis of drugs therefore shows in increase in oral bioavailability of drugs.

MATERIAL AND METHODS

Selexipag, Microcrystalline Cellulose Mannitol Spray Dried Lactose, Croscarmellose Sodium Crospovidone Sodium Starch Glycolate Pregelatinized Starch Polyvinyl Pyrrolidone Low Substituted Hydroxypropyl Cellulose, Aspartame Pearlitol, Magnesium Stearate, Talc

EVALUATION [6-9]

PRE-COMPRESSIONAL PARAMETERS

Bulk density

It is a ratio of mass of powder to bulk volume. The bulk density depends on particle size distribution, shape and cohesiveness of particles. Accurately weighed quantities of powder mixture were poured into graduated measuring cylinder. The measuring cylinder was then tapped 3 times on a hard surface from height of 2-3 inches at 2 second interval till a constant volume was obtained. It was expressed in gm/ml and given by

Bulk density = Weight of powder / Bulk Volume

Tapped density

The measuring cylinder containing known amount of blend is tapped for a fixed time. The minimum Volume occupied in the cylinder after tapping and weight of blend is measured. Calculate the tapped bulk density in gm/ml by thefollowing formula,

Tapped density = Weight of powder / Tapped Volume

Carr's Index / Compressibility Index (Table 1)

Carr's Index explains flow properties of the

tablet powder. It is expressed in percentage and given by

Carr's Index= Tapped Density- Bulk Density/ Tapped Density x 100

Table 1: Carr's Index

Carr's Index	Flow
5-12	Excellent
13-16	Good
17-21	Fair
≥ 40	Poor

Hausner's Ratio

It was determined by using the bulk density and tapped density values using following formula:

Hausner's Ratio = Tapped density / Bulk density

Table 2: Hausner′ s ratio

Hausner's Ratio	Flow Property
1.00-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very Poor
≥ 1.60	Very, Very Poor

Angle of Repose (Table 3)

It is defined as the maximum angle possible between the surface of the pile of the powder and horizontal plane. To determine angle of repose fixed funnel method was used. A funnel was fixed with its tip at a given height of 3 cm above a flat horizontal surface to which a graph paper was placed. The powder blend was carefully poured through a funnel till the apex of the conical pile just touches the tip of the funnel. The 'r' was calculated from the circumference obtained on the graph. θ was calculated by following formula;

- **$\tan \theta = h/r$**
- **$\theta = \tan^{-1} (h/r)$**

where,

θ = Angle of Repose h = Height of Pile

r = Radius of the base of the pile

Table 3: Angle of Repose

Angle of repose	Flow Property
<25	Excellent
25-30	Good
30-40	Fair
>40	Poor

POST-COMPRESSIONAL PARAMETERS

Thickness

The thickness of a tablet is determined by the diameter of die, the amount of fill permitted to enter the die, the compaction characteristics of the fill material, and the force or pressure applied during compaction. The crown thickness of individual tablet may be measured with a micrometer, which permits accurate measurements and provides information on the variation between tablets. The tablet

thickness was measured using vernier caliper.

Hardness

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. In addition, tablet should be able to withstand reasonable abuse when in hands of consumer. The relationship between hardness to disintegration and perhaps to drug dissolution release rate has become apparent. The hardness of the tablets was determined by means of Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly selected from each formulation and the mean and standard deviation values were calculated.

Friability

Tablets durability may be determined through the use of a friabilator. This apparatus determines the tablets friability or tendency to crumble, by allowing it to roll and fall within drum. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). 6.5 gm tablets were initially weighed (W initial) and transferred into friabilator. The friabilator wasoperated at 25 rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (W final). The percentage friability was then calculated by using following formula:

% Friability = [(W initial – W final) / W final] * 100

% Friability of tablets less than 1% is considered acceptable.

Wetting time

A piece of tissue paper folded twice was placed in a small petridish (internal diameter = 6.5 cm) containing 10 ml of Distilled water. A tablet was placed on the paper, and the time required for complete wetting was measured. Water absorption ratio was determined by using the formula.

R = 100 (Wa – Wb) / Wb

Where, Wb and Wa are the tablet weight before and after water absorption. Three trialsfor each batch were performed;

***In vitro* Disintegration test**

The process of breakdown of a tablet into smaller particles is called as disintegration. Disintegration of RDT was generally occurring due to water uptake by superdisintegrant via capillary action, which results in swelling of superdisintegrants and tablet get disintegrated. In the present study disintegration test was carried out on six tablets using the apparatus specified in IP (Electrolab disintegration apparatus IP). The distilled water at 37±2was used as a disintegration medium and time in second taken for complete disintegration of the tablet with no palpable mass left

behind in the apparatus was measured.

Weight variation

Twenty tablets were weighed individually and average weight was calculated. The individual weights were then compared with average weight. Not more than two of the individual weights should deviate from the average weight by more than 5%.As per IP **(Table 4)**.

Table 4: Weight Variation tolerance for uncoated tablets

Average weight of tablets (mg)	Maximum difference allowed (%)
Less than 80 mg	10 %
80 mg to 250 mg	7.5 %
More than 250 mg	5 %

PRELIMINARY SCREENING

A) FORMULATION OF PRELIMINARY BATCHES FOR SELECTION OF SUPER-DISINTEGRANT (Direct Compression)

The oral sublingual tablets were prepared using Selexipag using composition as depicted in following **Table 5**. Required amount of ingredients except magnesium stearate and talc were taken and sifted through sieve # 30. Magnesium stearate and talc were passed through # 60 and mixed to above blend and mixed uniformly for 30 minutes to form a homogenous mixture. The tablets were prepared by punching the above final blend in a tablet punching machine. The following **Table 5** shows preliminary trial batches composition for selection of super disintegrant.

Table 5: Preliminary batches for selection of superdisintegrant

Ingredients (mg)	P1	P2	P3	P4	P5	P6
Selexipag	0.20	0.20	0.20	0.20	0.20	0.20
Mannitol	59.00	58.00	57.00	59.00	58.00	57.00
MCC	10.00	10.00	10.00	10.00	10.00	10.00
Crospovidone	2.00	3.00	4.00	-	-	-
CroscarmelloseSodium	-	-	-	2.00	3.00	4.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00	1.00
Talc	0.80	0.80	0.80	0.80	0.80	0.80
Aspartame	2.00	2.00	2.00	2.00	2.00	2.00
Total Weight (mg)	75.00	75.00	75.00	75.00	75.00	75.00

B) FORMULATION OF PRELIMINARY BATCHES FOR SELECTION OF DILUENT (Direct Compression)

The sublingual tablets were prepared using Selexipag using composition as depicted in following **Table 6**. Required amount of ingredients except magnesium stearate and talc were taken and sifted through sieve # 30. Magnesium stearate and talc were passed through # 60 and mixed to above blend and mixed uniformly for 30 minutes to form a homogenous mixture. The tablets were prepared by punching the above final

blend in a tablet punching machine. The following **Table 6** shows preliminary trial batches composition for selection of Diluent.

Table 6: Composition of batches for selection of diluent ratio

Ingredients (mg)	D1	D2	D3	D4	D5
Selexipag	0.20	0.20	0.20	0.20	0.20
Mannitol	67.00	47.00	33.50	20.00	0.00
MCC	0.00	20.00	33.50	47.00	67.00
Crospovidone	4.00	4.00	4.00	4.00	4.00
Magnesium Stearate	1.00	1.00	1.00	1.00	1.00
Talc	0.80	0.80	0.80	0.80	0.80
Aspartame	2.00	2.00	2.00	2.00	2.00
Total Weight (mg)	75.00	75.00	75.00	75.00	75.00

DISSOLUTION PROFILE COMPARISON WITH MARKETED PRODUCT

In Vitro drug release comparison of formulation F9 with Uptravi® was performed by using USP type II apparatus in phosphate buffer pH 6.8 medium for 45 minutes with the temperature maintained at 37±0.5and stirring speed of paddle was adjusted to50 rpm. 5ml aliquots were withdrawn at 2,4,6,8,10,15,30 and 45 minutes and replaced by 5 ml of fresh phosphate buffer pH 6.8 media. The collected samples were analyzed at wavelength 294nm.

STABILITY STUDY

The optimized formulation F9 was monitored up to 1 month at accelerated stability conditions of 40±2 and 75±5 % RH. The tablets were scaled in aluminum foil and kept in humidity chamber. Sample were withdrawn after 1 month and characterized for % drug content, disintegration time and *in vitro* drug release.

RESULT AND DISCUSSION

EVALUATION OF PRE-COMPRESSION PARAMETER

From result it was found that angle of repose (24.44±0.24 to 26.19±0.26), Hausner's ratio (1.16±0.02 to 1.56±0.01) and carr's index (13.46±0.45 to 15.79±0.53) as depicted in above **Table 7**, which shows that all formulation had good flow property and compressibility.

EVALUATION OF POST-COMPRESSION PARAMETER

From result it was found that the tablets prepared for preliminary batches have hardness (2.3±0.2 to 2.7±0.3), Friability (0.19±0.07 to 0.26±0.08), thickness (3.11±0.08 to 3.19±0.12) and weight variation (74.8±0.8 to 76.4±0.2) as depicted in above **Table 8**, which shows that all formulation had good property.

From result it was found that the tablets prepared for preliminary batches have Disintegration time (22±1.07 to 35±1.21), Wetting time (20±2.05 to 28±2.33) and Drug content (96.98±0.75 to 98.87±0.21) as depicted in above **Table 9**, which shows that all formulation had good property. Evaluation of pre-formulation batches show that Crospovidone 4% show minimum disintegration time than other

superdisintegrats and good wetting property. So, it is optimized concentration used for further study.

IN-VITRO DRUG RELEASE

From the *In Vitro* dissolution study of preliminary trial batches it was found that all formulation show good drug release. P3 formulation show 85% of drug release in just 6 minutes and more than 90% of drug release in just 8 minutes.

ACCELERATED STABILITY STUDY OF THE OPTIMIZED BATCH

The optimized formulation was maintained at 40±2 and 75±5 % RH for one month (Optimized Formulations are kept in stability chamber for on-going stability study). The optimized formulation (n=3) stored at 40±2 and 75±5 % RH were found to be stable. At the end of the studies, samples were analyzed for the % Drug content, Disintegration time and *In Vitro* Drug release in **Table 10, 11**. There was not any change in morphological condition during stability study and also not any measurable change in the remaining parameter. Hence, the results of stability studies reveal that the optimized formulation has good stability.

Table 7: Evaluation of Pre-Compression Parameter of P1 to P6 batches

Batch	Bulk Density (gm/ml)	Tapped Density (gm/ml)	Carr's Index(%)	Hausner's Ratio	Angle of Repose
P1	0.46±0.02	0.54±0.01	14.81±0.56	1.17±0.03	25.82±0.25
P2	0.45±0.02	0.52±0.02	13.46±0.45	1.56±0.01	25.57±0.27
P3	0.49±0.01	0.57±0.02	14.04±0.51	1.16±0.02	24.44±0.24
P4	0.49±0.02	0.58±0.01	15.52±0.48	1.18±0.01	24.78±0.21
P5	0.48±0.01	0.57±0.02	15.79±0.53	1.19±0.02	26.19±0.26
P6	0.47±0.01	0.55±0.01	14.55±0.57	1.17±0.02	25.11±0.24

All Value are mean SD, * n=3

Table 8: Evaluation of Post-Compression Parameter of P1 to P6 batches

Batch	Thickness(mm)	Hardness(kg/cm2)	Friability(%)	Weight variation (mg)
P1	3.16±0.07	2.7±0.3	0.19±0.07	76.4±0.2
P2	3.19±0.12	2.4±0.4	0.22±0.06	75.8±0.4
P3	3.11±0.08	2.3±0.2	0.23±0.09	75.4±0.8
P4	3.14±0.06	2.5±0.3	0.24±0.05	76.2±0.2
P5	3.12±0.09	2.3±0.4	0.26±0.08	74.8±0.8
P6	3.15±0.10	2.6±0.2	0.20±0.10	75.2±0.4

All Value are mean SD, * n=3

Table 9: Evaluation of Post-Compression Parameter of P1 to P6 batches

Batch	Disintegration Time(Sec)	Wetting Time(Sec)	Drug Content(%)
P1	35±1.21	28±2.33	97.84±0.17
P2	26±1.12	23±1.25	96.98±0.75
P3	22±1.07	20±2.05	98.87±0.21
P4	27±1.09	24±1.58	98.04±0.98
P5	24±1.15	21±1.61	98.24±0.45
P6	32±1.22	21±1.48	97.54±0.69

All Value are mean SD, * n=3

Table 10: *In-Vitro* drug release of P1 to P6

Time (min)	P1	P2	P3	P4	P5	P6
0	0	0	0	0	0	0
2	55.15±1.07	48.32±0.93	62.35±1.14	44.5±1.06	56.3±0.75	57.24±1.13
4	69.23±0.98	61.78±0.68	74.74±0.87	62.45±1.10	70.97±0.84	68.83±1.04
6	77.54±0.74	75.45±0.73	85.36±1.04	76.61±0.58	82.31±0.91	82.49±0.87
8	89.49±0.81	86.73±1.25	99.64±0.95	87.56±0.87	91.68±1.15	88.67±0.64
10	94.91±1.10	94.64±1.05	-	95.58±1.24	96.32±0.94	93.49±0.82
12	97.81±0.69	99.98±0.98	-	98.72±1.02	99.02±1.08	99.61±0.96
14	99.12±0.45	-	-	99.66±0.34	-	-

All Value are mean SD, * n=3

Table 11: Comparative *In-Vitro* drug release study of formulation

% *In Vitro* Drug Release		
Time (min)	Initial	After 1 Month
0	0±0.00	0±0.00
2	70.02±0.67	62.84±0.94
4	84.54±0.98	80.46±0.28
6	99.81±0.86	97.18±0.45
8	-	-
10	-	-
12	-	-
14	-	-

All Value are mean SD, * n=3

CONCLUSION

Selexipag is a selective prostacyclin (IP, also called PGI2) receptor agonist of Pulmonary Arterial Hypertensive agent was used for present investigation. Selexipag is used for treatment for

Pulmonary Arterial Hypertension. Selexipag as sublingual drug delivery may be an advantageous from for treatment of Pulmonary Arterial Hypertensive Disease. So, In the present research work, an attempt has made to formulate sublingual tablets of Selexipag. The sublingual tablets were formulated using Crospovidone, Mannitol and MCC. From the present study it can be concluded that optimized formulation has enough % *In-vitro* Drug Release, It will comes directly in contact with sublingual mucosa and avoid first pass metabolism and improve bioavailability. The stability study was carried out as per ICH guideline to meet the desirable characteristics. In a nut shell, A Sublingual tablet of Selexipag was Successfully Formulated.

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