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Research Article

Formulation And Evaluation of Terbutaline Sulphate Tablet in The Sublingual Route for The Treatment of Asthma

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Conflict of interest: Nil

Abstract:

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 super disintegrant and sodium lauryl Sulphate as permeability enhancers by drug dispersion direct compression method. The formulation F1 found the drug permeability, 8 seconds disintegration time and drug release within one minute. The formulation F4 also has 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 or lactose monohydrate and Microcrystalline cellulose pH 102 in combination as filler, Crospovidone a super disintegrant, and Sodium Lauryl sulphate as permeability enhancer by direct compression drug dispersion method.

Keywords: Dispersion method, drug permeability, sublingual, super disintegrant.

Introduction

The sublingual route is a promising alternative for systemic drug delivery, offering improved patient compliance, robustness, and accessibility, with the added benefit of easy dose removal in emergencies [1,2]. This route bypasses the first-pass metabolism, making it ideal for drugs like cardiovascular medications, analgesics, steroids, barbiturates, enzymes, vitamins, peptides, and minerals. Current research focuses on developing advanced delivery systems and enhancing permeation to maximize efficiency. Sublingual delivery ensures rapid absorption and onset of action, making it particularly effective for drugs requiring immediate therapeutic effects, while also improving bioavailability and minimizing metabolic degradation in the liver [3,4]. Research on rapid-release delivery systems focuses on addressing oral cavity disorders for both local and systemic treatment. The unique anatomy and physiology of the sublingual mucosa facilitate efficient drug absorption. Current studies explore mechanisms and strategies for sublingual permeation enhancement to improve drug efficacy. Historical and modern theories of sublingual delivery are reviewed, offering insights into its evolution. Various dosage

forms, including those in development, are also analyzed for their effectiveness and practicality. These advancements highlight the potential of sublingual systems to provide fast, efficient, and patient-friendly drug delivery solutions for diverse therapeutic needs [5,6].

Methodology

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 super disintegrants, 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.

Sr. No.	Ingredient's	F1	F2	F3	F4	F5	F6	F7	F8	F9
1	Terbutaline sulphate I.P.	2	2	2	2	2	2	2	2	2
2	Mannitol I.P.	75.2	25.3	-	-	67.2	23.6	75	-	-
3	MCC (pH 102) IP	23.7	73.58	71.2	24.3	-	-	-	-	75
4	Lactose Monohydrate. I.P.	-	-	24.6	71.2	23.6	71.2	-	75	-
5	Maize starch B.P.	-	-	-	-	-	-	7.25	7.65	7.2
6	Crospovidone B.P.	6	6	6	6	6	6	6	6	6
7	Sodium lauryl sulphate B.P.	2	2	2	2	2	2	2	2	2
8	Purified Talc IP	2	2	2	2	2	2	2	2	2
9	Magnesium Stearate IP	2	2	2	2	2	2	2	2	2
10	Colloidal Silicon Dioxide IP	2	2	2	2	2	2	2	2	2
11	Aspartame I.P.	2	2	2	2	2	2	2	2	2
12	flavour	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3	0.3

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 onlyto study the effect of diluents on tablet characteristics and forselection of diluent for further formulations of tablets.From this step, it was concluded that the mannitol, microcrystalline cellulose pH 102, and lactose monohydratein ratios of 75% and 25% are suitable for further preparation of sublingual tablet.

Sr. No.	Ingredient's	F1	F2	F3	F4	F5	F6	F7	F8	F9
1.	Mannitol I.P.	98	-	-	69.38	31.5	70.29	31.26	-	-
2.	Microcrystallin e Cellulose (pH 102) IP	-	96	-	32.56	78.28	-	-	79.35	26.35
3.	Lactose Monohydrate. I.P.	-	-	98	-	-	31.25	65.37	31.59	75.38
4.	Purified Talc IP	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
5.	Magnesium Stearate IP	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
6.	Colloidal Silicon Dioxide IP	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

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.

Direct compression

The DC of tablet performed into three steps:

Dry mixing

The diluent passes 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 12 stations. WithD tooling punch sets.Wet granulation The Wet granulation process performed into three steps.

Dry mixing and granulation

Weighed the diluent 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.

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.

Drug dispersion

Terbutaline sulfate was dissolved in distilled water anddispersed onto the diluent Wet mass was passedthrough 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 wasobserved about 0.5% (on IR at 105°C for 5 min).

Dry mixing

The other diluent crospovidone passed through mesh 40 ss screen and blended.

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.

Stability study

Sublingual tablets of terbutaline sulphate formulated in the present study were subjected to the accelerated stability study. The stability studies of the formulated tablets were carried out at 40 0 c, RH 75% and at room temperature for one month. The effect of temperature and time on the physical characteristics of the tablets was evaluated for assessing the stability of the prepared formulations. The stability studies were carried out when the room temperature was 20 to 25 ^{o} c. The different parameters that were studied are in vitro disintegration time, wetting time, drug content, % drug permeability study and in vitro dissolution time.

RESULTS AND DISCUSSIONS

Preformulation study:

To ensure the compatibility of drug with excipients the IR spectra for pure drug and prepared granules was obtained and analyzed for principal peaks. The peaks obtained in prepared granules of formulations were almost identical to those obtained for pure drug reveling that there was no interaction between drug and excipients used in formulations.

Compatibility study

Compatibility study were performed for physical observations and confirmed by using IR spectrophotometer. The IR spectrum of the pure drug and physical mixture of the drug and polymer were studied. The characteristics absorption peaks of terbutaline Sulphate were obtained at following wavelengths**.**

Summary And Conclusion

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, % permeability, invitro dissolution time, content uniformity and drug content. 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 finally rapidly disintegration tablets were prepared by using mannitol, microcrystalline cellulose pH102 (F1) and lactose monohydrate, microcrystalline cellulose pH102 (F4) as filler, Crospovidone as superdisintegrant and sodium lauryl Sulphate as permeability enhancers. The total 9 formulations were prepared and evaluated for hardness, friability and weight variation, content uniformity, wetting time, disintegration time, % permeability and invitro drug release. All the formulations found the evaluation results within the limit. The formulation F1 found drug permeability, 8 seconds disintegration time and 96.95% drug release with in one minute. The formulation F4 also found the 98.25% of drug permeability, 13 seconds disintegration time and 90.31% drug release with in 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 super disintegrant, direct compression drug dispersion method and Sodium Lauryl

sulphate as permeability enhancer which enhance the sublingual permeability of drug.

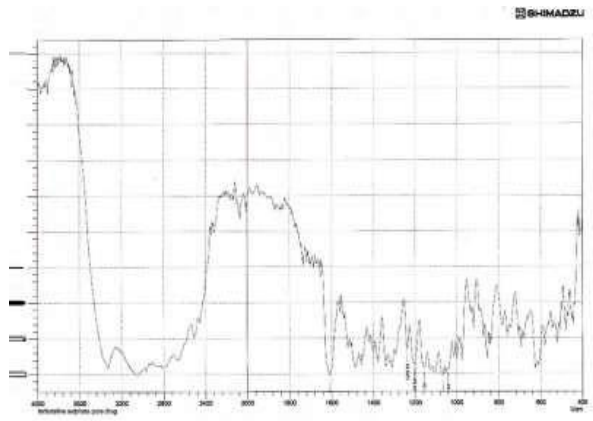


Figure 1. Terbutaline sulphate pure drug

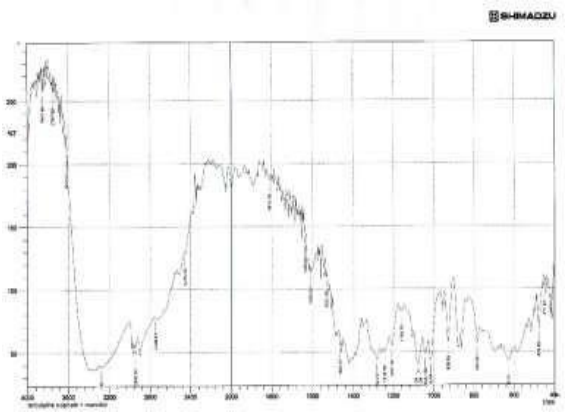


Figure 2. IR spectrum of terbutaline sulphate and mannitol

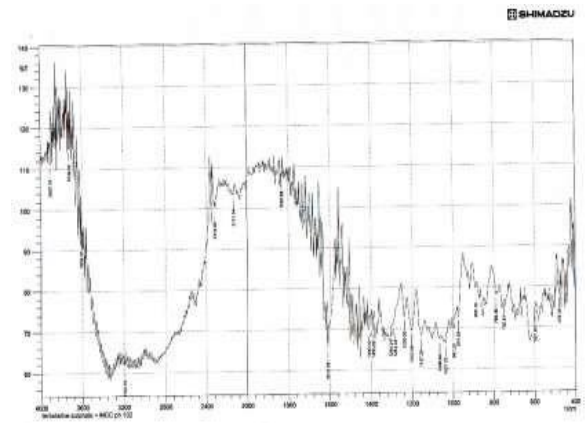


Figure 3. IR spectrum of terbutaline sulphate and microcrystalline cellulose pH 102

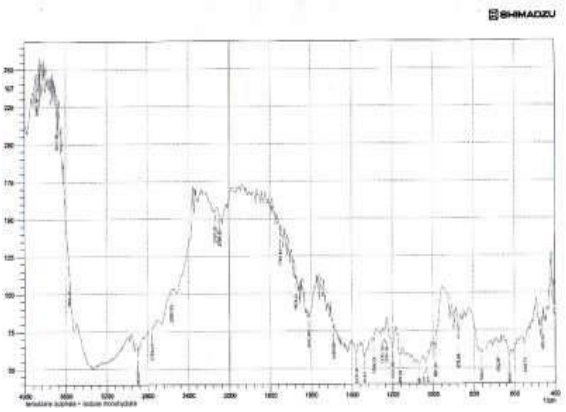


Figure 4. IR spectrum of terbutaline sulphate and lactose monohydrate

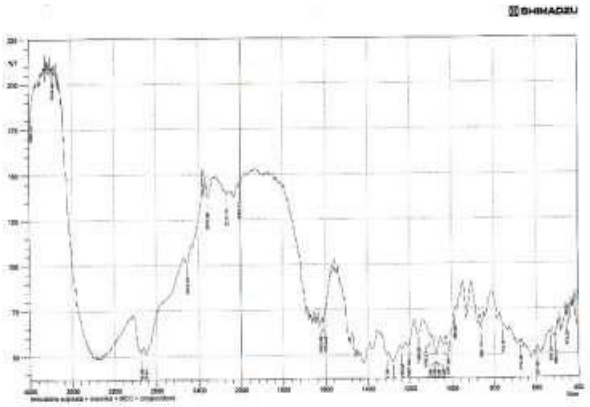


Figure 5. IR spectrum of terbutaline sulphate + mannitol + MCC pH102 + crospovidone

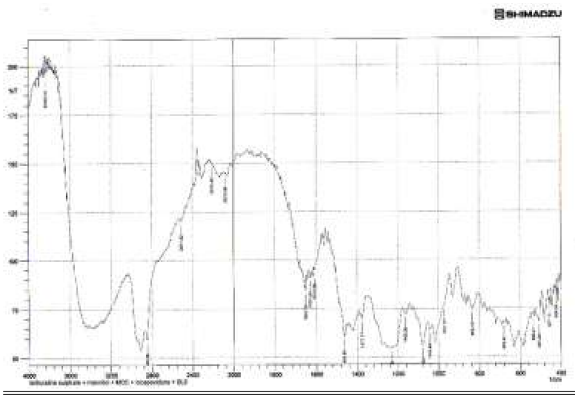


Figure 6. IR spectrum of terbutaline sulphate + mannitol + MCC pH102 + crospovidone + SLS

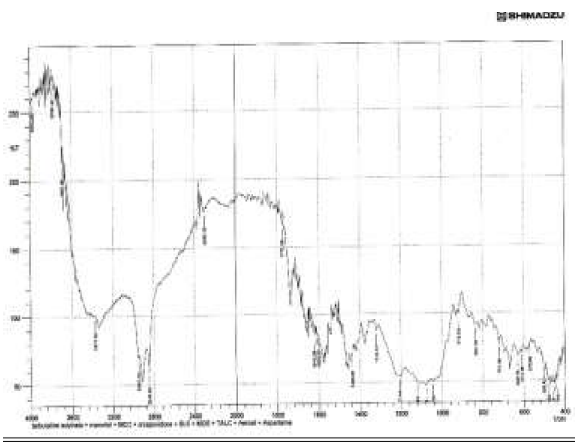


Figure 7. IR spectrum of terbutaline sulphate + mannitol + MCC pH102 + crospovidone + SLS + MGS + Talc + aerosol + aspartame

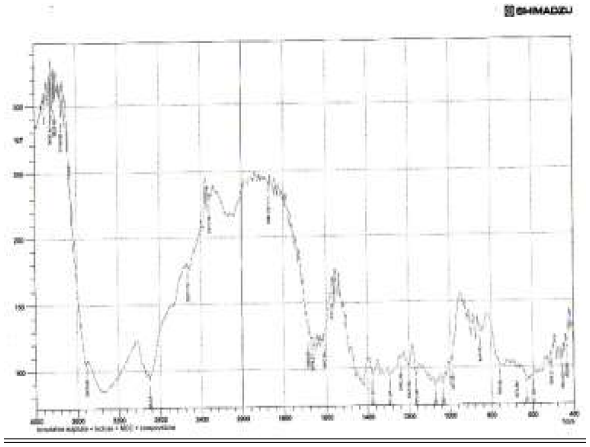


Figure 8. IR spectrum of terbutaline sulphate + lactose + MCC pH102 + crospovidone

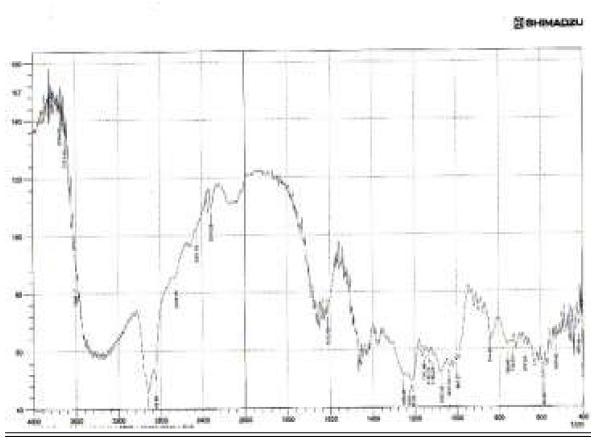


Figure 9. IR spectrum of terbutaline sulphate + lactose + MCC pH102 + crospovidone + SLS

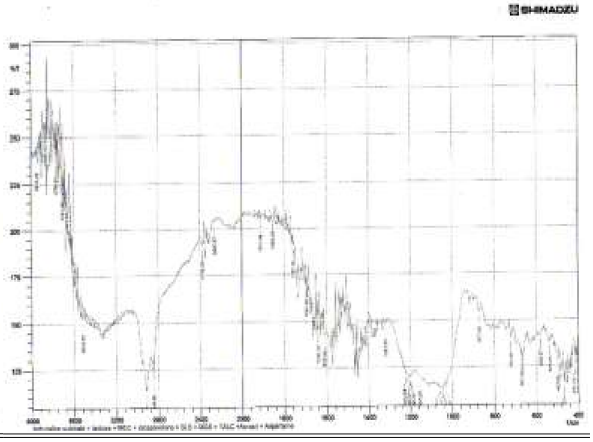
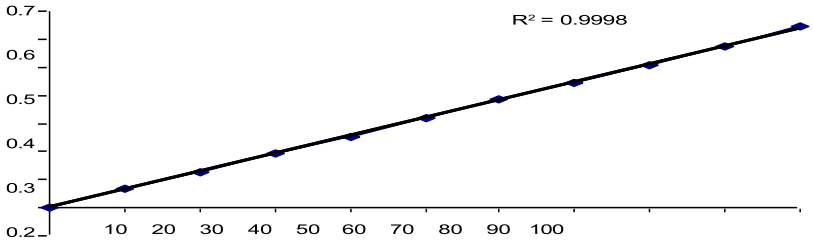


Figure 10. IR spectrum of terbutaline sulphate + lactose + MCC pH102 + crospovidone + SLS + MGS + Talc + aerosol + aspartame

Standard curve of Terbutaline Sulphate



Precompression parameter

Table 1. Evaluation Parameters of Granules of Terbutaline Sulphate

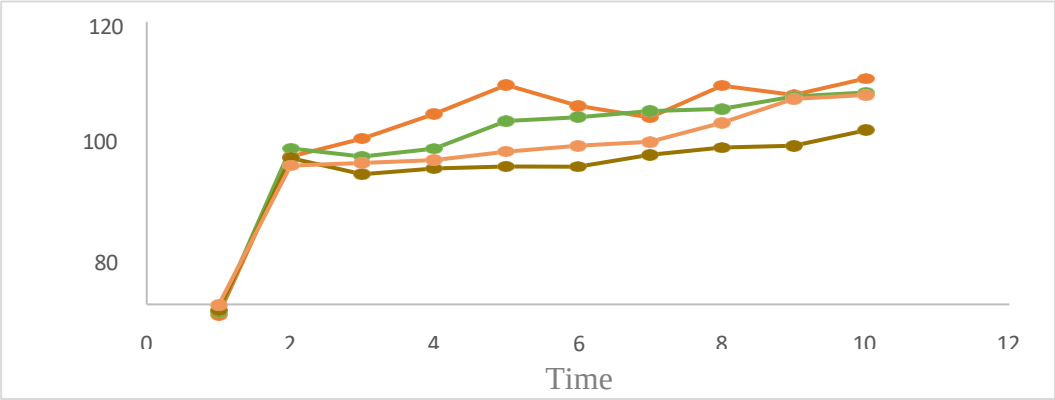
Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Loss on drying ,%	0.7	1.3	1.3	0.7	0.7	0.7	1.3	1.8	0.9
Angle of repose	$14^0$92’	$17^0$19’	$16^0$38’	$16^0$62’	16038	$15^0$31’	$15^0$87’	$16^0$12’	$16^0$21’
Bulk density, g/cm^3	0.5263	0.4347	0.4166	0.5263	0.625	0.5555	0.5555	0.5555	0.4243
Tapped density, g/cm^3	0.625	0.5263	0.5263	0.625	0.7142	0.625	0.625	0.625	0.526
% compressibility	15.79	17.4	20.84	15.79	12.5	11.12	11.12	11.12	19.33
Hausner ratio	1.2	1.36	1.78	1.29	1.35	1.29	1.67	1.37	1.04

Evaluation of Tablets

Table 2. Evaluation Parameters of Sublingual Tablets of Terbutaline Sulphate

Parameters	F1	F2	F3	F4	F5	F6	F7	F8	F9
Hardness, kg/cm2	2	3	3	3	2.5	3	3.5	4	3
Thickness, mm	2.67	2.95	2.25	2.44	2.36	2.88	2.36	2.89	2.67
Weight variation, avg, wt. mg	100.2	100.1	99.75	100.85	100.35	101.5	101.25	102.85	101.28
% friability	0.02	0.007	0.004	0.01	0.25	0.037	0.072	0.095	0.09
Disintegration time (sec)	8	8	7	13	15	14	18	35	15
Wetting time, seconds	5	7	7	8	11	13	18	41	12
% drug permeability	46.4	45.45	49.63	43.12	43.72	55.23	59.67	76.59	89.33
% drug release (1min).	96.95	81.47	82.57	90.31	95.84	81.1	94	90.31	85.52
% drug content	93.73	93.79	98.96	95.82	93.9	93.75	95.83	97.44	93.8
± S.D.	± 0.51	± 0.56	± 1.32	± 0.21	± 0.45	± 0.51	± 0.22	± 0.79	± 0.49
Content uniformity,%	95.29	91.85	93.73	97.89	91.07	87.9	106.3	96.23	95.18
± S.D.	± 5.2	± 1.64	± 0.98	± 5.1	± 1.92	± 3.29	± 3.46	± 0.09	± 0.47

In-vitro drug release study



Stability Studies of Optimized Batch F1 & F4

Table 3. Stability Parameters of Formulation F1 & F4 Stored at Room Temperature (25 0 c and 65% RH)

Parameters	F1			F4		
	Controlled	After 1 Month	After 3 month	Controlled	After 1 month	After 3 month
Drug content %	94.59%	95.90%	96.49%	94.82%	95.50%	96.16%
Disintegration time (s)	9	9	9	12	12	11
Wetting time, seconds	7	8	7	10	9	9
% drug permeability	94.41%	95.15%	93.26%	97.20%	92.19%	91.59%

Table 4. Stability Parameters of Formulation F1 & F4 Stored At Temperature 400 & RH 75%.

Parameters	F1			F4		
	Controlled	After 1 month	After 3 months	Controlled	After 1 month	After 3 months
Drug content %	95.69%	94.12%	96.19%	96.17%	95.39%	99.64%
Disintegration time(s)	9	8	8	12	11	11
Wetting time (s)	8	7	7	9	9	9
% drug permeability	94.58%	95.15%	92.36%	98.17%	94.18%	96.49%

Table 5. In Vitro Dissolution Profile of Formulation F1 & F4 Stored At Room Temperature

	% drug release F1			% drug release F4		
Time in minutes	Controlled	After 1 month	After 3 month	Controlled	After 1 month	After 3 month
1	89.67%	91.28%	95.95%	90.29%	94.36%	95.67%
2	85.67%	87.69%	88.67%	81.29%	89.64%	91.22%
3	71.29%	81.29%	89.37%	89.67%	90.19%	94.35%
5	67.39%	75.39%	80.29%	65.37%	71.29%	85.37%

Table 6. In Vitro Dissolution Profile Of Formulation F1 & F4 Stored At Temperature 40^0 & RH 75%.

	% drug release F1			% drug release F4		
Time in minutes	Controlled	After 1 month	After 3 month	Controlled	After 1 month	After 3 month
1	94.29%	95.37%	92.39%	95.67%	96.58%	98.67%
2	72.39%	82.37%	85.49%	81.29%	89.67%	91.29%
3	79.68%	81.29%	85.69%	86.68%	89.67%	91.29%
5	78.90%	79.68%	81.29%	65.97%	75.69%	82.39%

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