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DESIGN AND EVALUATION OF OPTIMIZED FAST DISSOLVING TABLETS OF SALBUTAMOL SULPHATE

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Abstract

The objective of the current study is to develop salbutamol sulphate fast dissolving tablet possessing higher degree of bioavailability due to presence of superdisintegrants, which tend to dissolve tablet rapidly in the saliva of mouth, rendering higher rate of dissolution. A 3^2 factorial design was used to investigate effect of amount of crospovidone and superdisintegrants namely cross-linked carboxyl methyl cellulose as independent variable. Friability, disintegration time, percent drug release was taken as dependent variables. Different concentrations (3%, 4%, 5%) of superdisintegrants cross-linked carboxyl methyl cellulose and crospovidone (5%, 10%, 15%) were used respectively. Tablets were prepared by direct compression method; the compressed tablets were dried for 6hours to allow sublimation of camphor and to increase the porosity of the tablets hence to improve their dissolution. The tablets were evaluated for hardness, thickness, friability, weight variation, porosity, wetting time, disintegration time, drug content and in-vitro drug release.

Drug-excipient interaction was investigated by FTIR study. Optimized formulation was further evaluated for stability as per ICH guideline. All tablets had hardness in the range of 3-3.5 kg/cm^2 and friability was less than 1.08%. Weight variation and drug content were within USP prescribed limits. FTIR study revealed no drug-excipient interaction. SEM study showed that the tablet surface morphology was porous. A stability study for optimized F3 formulation as per ICH guideline for 90 days showed no changes in drug content. Therefore, it may be concluded that optimized tablets of salbutamol sulphate possess high porosity which dissolve rapidly in mouth and hold high degree of bioavailability.

Keyword: Salbutamol sulphate, fast dissolving tablet, superdisintegrant, Optimization

Introduction

Salbutamol sulphate is a $\beta_{2,}$ receptor agonist widely used as bronchodilator to relieve acute as well as chronic attacks of asthma. Asthma is a complex genetic disorder involving the interplay between various environmental and genetic factors. It was selected as drug candidate as it is not available in such a dosage form[1]. Mouth dissolving tablet system can be defined as a tablet that disintegrates and dissolves rapidly in saliva within few seconds without need of drinking water or chewing[1].

In spite of tremendous development in drug delivery technology, oral route remains perfect route for administration of therapeutic reagents because of low cost of therapy, ease of administration, accurate dose, self-medication, pain avoidance, leading to high level of patient compliance. Tablets and capsules are the most popular dosage forms[2] but main drawback of such dosage forms is dysphasia or difficulty in swallowing. This problem led to development of novel solid dosage forms such as mouth dissolving tablets that disintegrate and dissolve rapidly in saliva without need of water.

Mouth dissolving tablets avoid first pass metabolism and enhance bioavailability of active ingredient[3].

Therefore an attempt was made in present study to formulate mouth dissolving tablets of Salbutamol sulphate by using superdisintegrant like cross-linked carboxy methyl cellulose (AC-di-sol) and crospovidone (polyplasdone XL)[4]. The aim was to optimize a rapid mouth dissolving formulation by 3^2 factorial designs and developing a dosage form with high porosity and enhanced bioavailability.

Materials

Salbutamol sulphate was obtained as gift sample from Micro Labs Ltd, Bangalore, India. Crospovidone, lactose, Sucralose[15], Kyron, crospovidone, Magnesium stearate, and Talc were procured as gift samples from Loba Chemie Ltd, Mumbai. Cross-linked carboxy methyl cellulose was received from Eros Pharma, India Ltd Bangalore.

Methods

Preparation of tablet blend

Tablets containing 25 mg of salbutamol sulphate were prepared by sublimation method. The various formulations used in the study are shown in Table 1. The drug, diluents, superdisintegrant, crospovidone and sucralose were passed through sieve # 40.

All the above ingredients were properly mixed together (in a poly-bag). Talc and magnesium stearate were passed through sieve # 80, mixed, and blended with initial mixture in a poly-bag. The powder blend was compressed into tablets on tablet machine (Cadmach single punch compression machine). Compressed tablets were subjected to the process of sublimation in vacuum oven (Rotek Oven) at 60^0C for 6 hour[5].

Table 1: **3^2 factorial design formulation of salbutamol prepared by sublimation method.**

Ingredient (mg)	Formulation code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Salbutamol sulphate	25	25	25	25	25	25	25	25	25
Cross-linked CMC	3	4	5	3	4	5	3	4	5
Camphor	5	5	5	10	10	10	15	15	15
Sucralose	2	2	2	2	2	2	2	2	2
Magnesium stearate	1	1	1	1	1	1	1	1	1
Talc	1	1	1	1	1	1	1	1	1
Crospovidone	63	62	61	58	57	56	53	52	51
Total weight	100	100	100	100	100	100	100	100	100

Evaluation of mouth dissolving tablets

The formulated rapid mouth dissolving tablets were evaluated for different parameters like drug content, thickness, weight variation test, hardness, friability, wetting time, disintegration time, dissolution test, porosity, and morphology by SEM. Tablet thickness was measured by using Vernier calipers. Five tablets were randomly taken and placed between two arms of Vernier caliper. The crushing strength (hardness) of tablets was measured by using Monsanto hardness tester[8]. Twenty tablets were picked up at random and average weight was determined using an electronic balance. Tablets were weighed individually and compared with average weight to determine weight variations[9].

Drug content: Ten tablets were powdered and blend equivalent to 25 mg of Salbutamol sulphate was weighed and dissolved in suitable quantity of phosphate buffer pH 6.8. The solution was filtered through 0.45 mm membrane filter and drug content was analyzed using UV Spectrophotometer (UV- 1700 Shimadzu) at λmax 277nm[7].

Friability test: The friability of tablets was measured in Roche friabilator. Twenty tablets were de-dusted at 25 rpm for 4 min and weighed again. Percentage friability was calculated from loss in weight as given in equation below. The weight loss should not be more than 1%.

$$\% \text{ Friability} = [(\text{Initial weight} - \text{Final weight})/\text{Initial weight}] \times 100$$

In- vitro disintegration test

The test was carried out on six tablets using digital tablet disintegration test apparatus (Electrolab). Distilled water at 37 ± 0.5^0C was used as a disintegration media and time in second taken for complete disintegration of tablet with no residue remaining in apparatus[10].

Table 2: Tablet weight (mg) before and after sublimation of camphor

Code	Camphor (mg)	Sublimation	
		Before (mg ± SD)	After (mg ± SD)
F1	5	100.2 ± 0.83	96.4 ± 0.51
F2	5	99.4 ± 0.89	96.46 ± 0.87
F3	5	99.8 ± 0.83	96.56 ± 0.56
F4	10	100.4 ± 0.89	91.03 ± 0.66
F5	10	99.6 ± 0.89	90.96 ± 0.20
F6	10	101.1 ± 0.70	91.03 v 0.34
F7	15	100.8 ± 0.41	86.33 v 0.65
F8	15	99.2 ± 0.48	85.26 ± 0.55
F9	15	101.8 ± 0.81	86.70 ± 0.45

In-vitro drug release study

Percent drug release of Salbutamol sulphate mouth dissolving tablets was determined by USP type-II apparatus (USP XXIII dissolution test apparatus) using paddle method[14]. The dissolution test was performed using 500 ml of phosphate buffer pH 6.8 at 37 ± 0.5^0C at 50 rpm. A sample of 5 ml solution was withdrawn from dissolution apparatus at regular interval of 30s. The same quantity of sample was replaced with fresh 5ml dissolution medium. The samples were filtered through 0.45 mm membrane filter. Absorbance of these samples was analyzed at λmax 277nm using UV-visible spectrophotometer[11].

Wetting time

Wetting time of tablets can be measured using simple procedure. Six circular tissue papers of 10cm diameter were placed in a petri-dish. 10 ml of water containing amaranth dye was added to petri-dish[16]. A tablet was carefully placed on the surface of tissue paper. Time required for water to reach upper surface of the tablet was noted as wetting time[13].

Measurement of tablet porosity

The porosity of tablets was calculated from the weight of tablet (W), tablet volume (V), and true density of powder (r) using following equation. True density of powder was determined by a pycnometer[12].

$$\% \text{ Porosity} = [1 - \text{weight of tablet (W)} / \text{Volume (V)} \times \text{Density } (\rho)]$$

Drug-excipient interaction study

FTIR spectra of all formulations were obtained on IR spectrophotometer (Shimadzu). The samples were prepared in KBr dish[19] (2 mg of sample in 200mg KBr). The samples were scanned in the range of 500 to 4000 cm^{-1}.

SEM analysis

The surface morphology of optimized formulation before and after sublimation of crospovidone was studied using (JSM-6360). The tablet surface was examined under Scanning Electron Microscopy[20].

Stability study: The stability of optimized formulation F3 was tested according to ICH guideline; at $40^0C \pm 2^0C$/75% RH ±5% condition in stability camber for 3 months. Stability studies on tablets were performed and drug content was estimated for 30, 60, and 90 days[18].

Experimental design: The 3^2 factorial designs were used for the optimization of rapid mouth dissolving tablets of Salbutamol sulphate. The two independent factors, concentration of cross-linked carboxyl methyl cellulose (X1) and concentration of crospovidone (X2), were set to three different levels and experimental trials were performed for all nine possible combinations. The dependent responses measured, were disintegration time, friability, and percent drug release[4, 17].

Validation of the experimental design

In order to validate the experimental design using a polynomial equation, three parameters namely disintegration time, friability and percent drug release were selected[21]. The second order polynomial equation was applied as a tool of mathematical modeling.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_1^2X_1X_2 + b_1^2X_1^2 + b_2^2X_2^2$$

Where, Y is the dependent variable, b0 is the arithmetic mean response of the nine runs and b1 (b_1,b_2,b_1^2,b_1^1 and b_2^2) is the estimated co-efficient for corresponding factor X1 (X_1,X_2,X_1^2,X_1^1,and X_2^2), which corresponds to the average results of changing one factor at a time from its low value to high value. The interaction term (X_1X_2) depicts the changes in the response when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity[17].

Table 03: Evaluation of factorial design for fast dissolving tablets.

Code	Hardness (kg/cm^2)	Thickness (mg ± SD)	Drug content (%±S.D)	In-vitro DT (sec ± SD)	Wetting time (sec ± SD)	Friability (%±SD)	% release (%SD)	% porosity (%±SD)
F1	3 -3.5	2.4±0.20	100.3 ± 0.3	30.16±0.98	28.33±0.36	0.33±0.12	75.01±0.05	12.75 ± 0.9
F2	3 -3.5	2.64±0.35	98.7±0.3	24.66±0.81	23.0±.67	0.34±0.10	78.1±0.09	13.10±0.78
F3	3 -3.5	2.33±0.30	101.3±0.7	19.16±0.85	17.16±0.47	0.32±0.10	85.21±0.55	15.38±0.69
F4	3 -3.5	2.36±0.20	98.83±0.1	27.5±0.76	24.66±.50	0.73±0.16	77.31±0.40	23.08±0.75
F5	3 -3.5	2.26±0.15	98.60±0.1	23.0±0.88	22.5±0.51	0.67±0.12	78.76±0.07	25.60±0.63
F6	3 -3.5	2.23±0.32	98.77±0.2	19.33±1.03	17.83±0.32	0.63±0.24	84.92±0.08	27.36±0.58
F7	3 -3.5	2.13±0.15	98.44±0.01	24.16±0.98	22.69±0.36	1.08±0.13	82.31±0.08	40.09±0.84
F8	3 -3.5	2.3±0.20	98.85±0.0	21.66±0.81	19.16±0.31	1.01±0.10	79.09±0.26	40.75±0.70
F9	3 -3.5	2.13±0.15	99.93±0.0	17.5±0.79	15.5±0.45	1.04±0.13	88.57±0.11	41.01±0.87

Table 4: Drug content of fast dissolving salbutamol sulphate tablets at $40^0C \pm 2^0C$/75% RH±5%

Physical parameter	Factorial batch F3			
	0 days	30 days	60 days	90 days
% Drug content	101.20±0.86	100.44±0.52	99.2±0.35	98.6±0.80

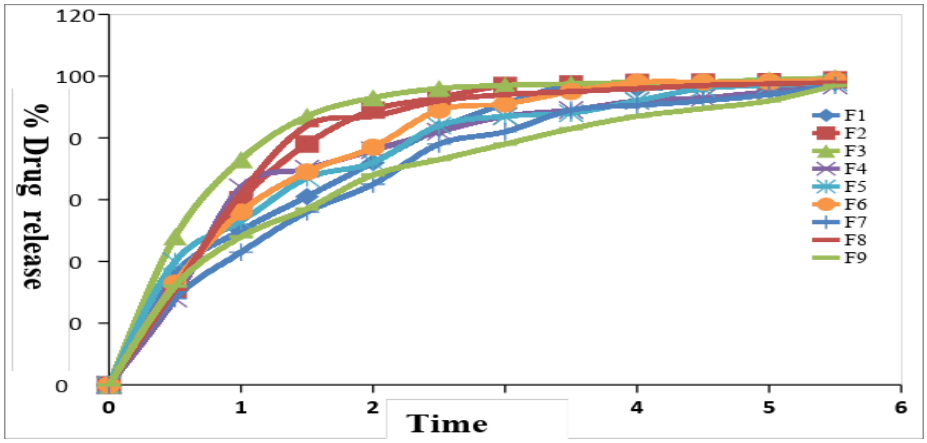

Fig 1: In-vitro dissolution profile of all formulation.

Result and discussion

The aim of current study was to optimize a rapid mouth dissolving formulation by 3^2 factorial designs for developing a dosage form with high porosity and enhanced bioavailability. The mean weight of all tablets decreased after sublimation, which corresponds to weight of crospovidone added as shown in Table 2. This study revealed that almost all of crospovidone had sublimated from the tablets.

The weight variation, hardness, friability, porosity, and drug content of all formulated tablets were found to be satisfactory as shown in Table 3. All the prepared tablets were of uniform weight with acceptable weight variation. Hardness of all formulations was 3-3.5 kg/cm^2 and friability loss of tablets was found to be between 0.32 and 1.08%. Drug content was found to be as high as (±98.44%) and uniform (coefficient of variation between 0.03 and 0.3%). The sublimating agent increased the friability of tablets probably by increasing porosity. The hardness and friability studies revealed that the tablets possessed good mechanical resistance.

In-vitro disintegration test

The most important parameter that needs to be optimized in the development of mouth dissolving tablets is the disintegration time of tablets. In present study all tablets disintegrated in less than 30s as shown in Table 3 fulfilling the official requirement (<1 min) for mouth dissolving tablets.

Wetting time

Rapid disintegration of prepared tablets in saliva may be related to an improvement in the ability of water to penetrate into tablet due to high porosity achieved by the increase in number of pores after sublimation of crospovidone. The outcome of this study was that many porous cavities were formed in tablets due to sublimation of crospovidone.

Porosity

Tablets exhibit % porosity in the range of 12.92-41.28 for crospovidone concentration in the range of 5-15mg. Hence many porous structures are responsible for faster water uptake hence reduced wetting time; it also facilitates wicking action of cross-linked CMC bringing about faster disintegration.

In-vitro dissolution test

Disintegration time of tablet decreases with increase in concentration of crospovidone and cross-linked CMC. Tablet showing lower disintegration time will show high drug release. In-vitro dissolution profile (Fig. 1) revealed faster and

maximum drug from formulation F3. Formulation F3 prepared by direct sublimation of crospovidone shows release of 99.89% drug at 2.5 min, from above data F3 formulation was found to be optimized and used for further stability study.

Stability study

Stability study performed on optimized F3 formulation as per ICH guideline for 90 days at 40^0C ± 2^0C/75% RH±5%. The study found that no remarkable changes in the physical properties of tablets as well as no change in drug content as indicated in Table 4.

Drug-excipient interaction study

The drug salbutamol sulphate exhibited four distinct peaks around 3000 cm^{-1}, a sharp peak appears at 3479 cm^{-1} corresponds to the vibration of primary alcoholic OH bond function present in the drug. Another alcoholic group present at the side chain of the drug as appeared 3320 cm^{-1} which is secondary OH group. The phenolic OH group present in the molecule has appeared 3166 cm^{-1} the secondary amine function present has given a peak at 3000 cm^{-1}. These observations are in confirmatory with the structure of the drug salbutamol sulphate. Hence above result conclude that no drug and excipients interaction was found.

Surface topography

The image shows formulation of pores on tablet surface that may have extended into the matrix after sublimation of the sublimating agent, thus providing a sufficiently porous structure to facilitate rapid penetration of dispersion medium. This is evident from the magnified tablet surface images (Fig. 2) of tablet before and after sublimation.

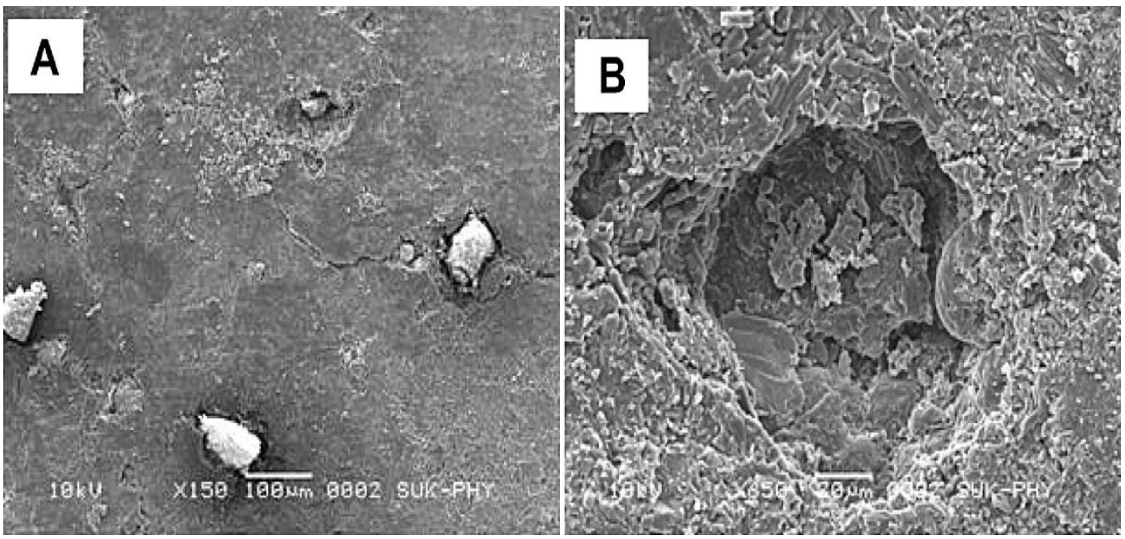

Fig. 2: SEM images of optimized formulation F3 before (A) & after Sublimation (B)

Validation of experimental design

The parameter disintegration time can be described by the model equation,

$$Y \text{ (disintegration time)} = +23.03 - 4.32X1 - 1.80X2 + 1.09X1X2$$

The negative sign for coefficient X1 and X2 indicates that as concentration of superdisintegrant increases, disintegration time decreases. R2 value 0.9926 for disintegration time indicating good correlation between independent and dependent variable. The term with ($P < 0.0001$) were considered significant. The parameter friability can be described by model equation,

$$Y \text{ (friability)} = +0.69 - 0.030X1 + 0.35X2$$

The negative sign for coefficient X1 indicates that as concentration of superdisintegrant increases friability decreases and positive sign of X2 indicates that as concentration of crospovidone increases friability also increases. R2 value 0.9955 for friability indicating good correlation between independent and dependent variable. The term with ($P < 0.0001$) were considered significant. The % drug release can be described by the model equation,

$$Y \text{ (\%Drug release)} = +79.31 + 2.88X_1 + 3.98X_2\ 2.67X_1X_2 + 1.54(X_1)^2 + 3.11\ (X_2)^2$$

The positive sign for X1 and X2 indicates that as concentrations of superdisintegrant increases, percent drug release also increases. R2 value 0.9789 for percent drug release indicating good correlation between independent and dependent variable. The term with ($P < 0.01$) were considered significant. The computer generated response surface for dependent variables are shown in Fig. 3 respectively.

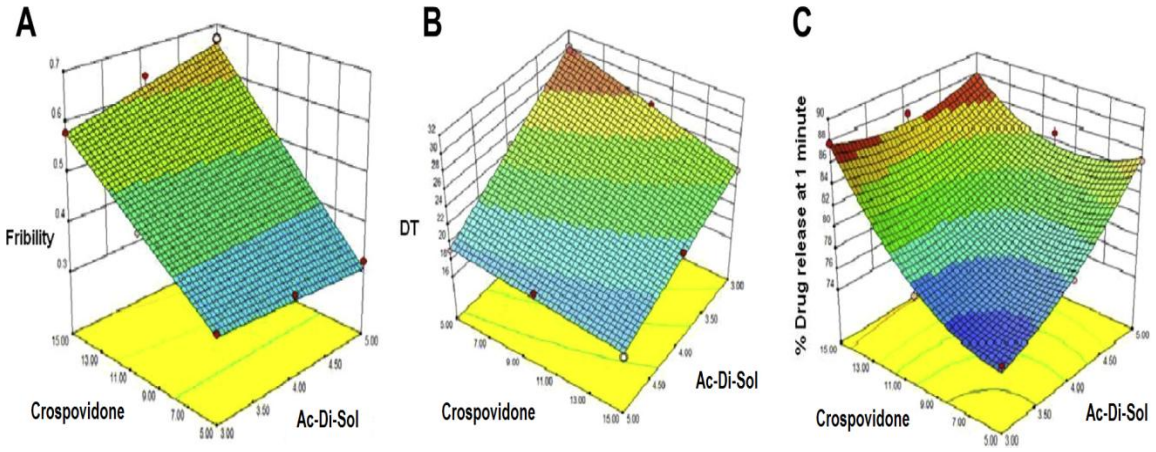

Fig 3: Response surface plot of factorial variable on

Friability (A), Disintegration time (B) and % drug release (C)

Conclusion

The formulation F3 using combine approach of sublimating agent and superdisintegrant was identified as optimized mouth dissolving tablet formulation of Salbutamol sulphate. It appears that the use of superdisintegrant in higher concentration results in faster disintegration of the tablets with low friability. Crospovidone used as sublimating agent, increases porosity of tablets due to which penetration of water takes place at high rate. This leads to faster disintegration of the tablets. Thus it can be concluded that the developed novel method for preparing rapid mouth dissolving tablets for salbutamol increases the porosity and enhances the bioavailability.

Conflict of Interest: We declared that this review does not have any conflict of interest.

References

1. Martindale the Complete Drug Reference, Thirty-Third Edition, Pharmaceutical, Press London, P-52: 2002.
2. Fu Y, Yang S, Jeong SH, Kimura S, Park K. Therapeutic drug carrier systems, orally fast disintegrating tablets: developments, technologies, taste-masking and clinical studies. Crit Reviews. 2004; 21(6): 433-475.
3. Kuchekar BS, Badhan AC, Mahajan HS. Mouth dissolving tablets of salbutamol sulphate: A novel drug delivery system. Indian Drugs, 2004; 41: 592-98.
4. Shenoy V, Agarwal S, Pandey S. Optimizing fast-dissolving dosage forms of diclofenac sodium by rapidly disintegrating agents. Indian J. Pharm. Sci., 2003; 65: 197-201.
5. Ishikawa T, Watanabe Y, Utoguchi N, Matsumoto M. Preparation and evaluation of tablets rapidly disintegrating in saliva containing bitter taste mask granules by the compression method. Chem. Pharm. Bull, 1999; 47(10): 1451-54.
6. Watanabe Y, Koizumi K, Kiriyama M, Matsumato Y. New compressed tablets rapidly disintegrating in saliva in the mouth using crystalline cellulose as disintegrants. Biol. Pharm. Bull, 1995; 18(9): 1308-1310.
7. Garg R and Sharma AK. Simultaneous determination of salbutamol and etofylline by third derivative ultraviolet spectroscopy. Indian J. Pharm. Sci., 1997; 59(6): 295-298.
8. The Pharmaceutical Codex: The Principle & Practice of Pharmaceutics, 12th Edition: 1041.
9. Roser BJ, Blair J. Rapidly soluble oral dosage form, methods of making the same and composition thereof. US patent 5762961. June 9, 1998.

10. Lachman L, Lieberman A, Kinig JL. The Theory and Practice of Industrial Pharmacy. Varghese Publishing House; 1991:67-68.
11. Indian Pharmacopoeia. 4th ed. vol 2. New Delhi: Controller of Publication, Govt. of India; 1996:736.
12. Battue SK, Repay MA, Maunder S, Rio MY. Formulation and evaluation of rapidly disintegrating tablet fenoverine tablets: effect of superdisintegrants. Drug Dev Ind. Pharm. 2007; 33: 1225-1232.
13. Swarbrick James. Encyclopedia of Pharmaceutical Technology, 3rd ed. vol 6. 1998:2614-2629.
14. Martin A, Chun AHC. Physical pharmacy. 5th ed. Lippincott Williams and Wilkins; 1994:286-289.
15. Masaaki S, Toru M, Shinji N, Koji M, Hiroyuki Y. Factors affecting the characteristics of rapidly disintegrating tablets in the mouth prepared by the crystalline transition of amorphous sucrose. Int Pharma. 2005; 296: 64-72.
16. Medwick T, Baliely LC. A procedure for conducting open-dish studies. Pharm Forum. 1998; 24: 6315-6316.
17. Singh J, Philip AK, Pathak K. Optimization studies on design and evaluation of Orodispersible pediatric formulation of indomethacin. AAPS Pharm Sci Tech. 2008; 9: 60-66.
18. British Pharmacopoeia, the Department of Health, Social Services & Public Safety, London, Vol. 1; 584.
19. Clarke J. Analysis of Drugs and Poisons, 3rd Ed. Edited by Anthony C Moffat, David M, Ossetton and Orian Widdop, Vol. 2: 1546-1547.
20. Ainley Wade, Paul J Welles. Handbook of Pharmaceutical Excipients, 2nd Edn. The Pharmaceutical Press, London, 1994, 483-88.
21. Pathan I.B, Formulation design and optimization of novel mouth dissolving tablets for venlafaxine hydrochloride using sublimation technique. J of Phar. Res, 2013; 6: 593-598.

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