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RESEARCH ARTICLE

Design, Development and Optimization Aceclofenac Effervescence tablets by Central Composite Design

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ABSTRACT:

The oral solid dosage forms are the most popular way of taking medication despite having some disadvantages like slow absorption and hence prolong onset of action. These problems can be overcome by some drug delivery system like mouth dissolving tablets, dispersible tablets, effervescent tablets, etc. Aceclofenac is often used to relieve the inflammation, swelling, stiffness and joint pain which sometimes required fast onset of action. Aceclofenac effervescent tablet was prepared to enhance onset of action. Tablets were prepared using anhydrous citric acid, tartaric acid and effervescent components by direct compression method. Solid dispersion of Aceclofenac with anhydrous lactose can be prepared to increase solubility of aceclofenac. The solid dispersions were evaluated for drug content, practical yield, solubility and DSC for drug complex study. Central composite design was used for optimization of aceclofenac effervescent tablet. The effervescent formulations were evaluated for physicochemical parameters, drug content, effervescent lag time, total effervescent time, in vitro drug release study, FTIR for compatibility and stability testing. Optimized formula showed more than 50 % drug release after 5 min and hence faster onset of action. The study point of aceclofenac effervescent tablet is ease of administration, accuracy of dosing and faster onset of action.

KEYWORDS: Aceclofenac, effervescent tablet, central composite design, solid dispersion.

INTRODUCTION:

Effervescent tablet is a tablet intended to be dissolved or dispersed in water before administration. It generally contains in addition to active ingredients, mixture of acids/acid salts (citric, tartaric, malic acid or any other suitable acid or acid anhydride) and carbonate and hydrogen carbonates (sodium, potassium or any other suitable alkali metal carbonate or hydrogen carbonate) which release carbon dioxide when mixed with water. Occasionally, active ingredient itself could act as the acid or alkali metal compound necessary for effervescent reaction. Effervescent tablets are uncoated tablets that generally contain acid substances and carbonates or bicarbonates and which react rapidly in the presence of water by releasing carbon dioxide. They are intended to be dissolved or dispersed in water before use. [1, 2]

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Effervescent tablet has many advantages like fast onset of action (as the tablet is pre dispersed and is in the form of solution at the time of consumption), no need to swallow tablets (as they are administered in liquid form), good stomach and intestinal tolerance (they dissolve fully in a buffered solution, hence reduced localized contact in the upper gastrointestinal tract leads to less irritation and greater tolerability), Improved palatability (taste of bitter drugs can be masked by adding taste masking agents, colors and flavors), stability, more consistent response (reproducible pharmacokinetic profiles), accurate dosing, improved therapeutic effect (They help in solubilization of poorly soluble drugs). [3-9]

Aceclofenac (ACF) is non steroidal anti-inflammatory (NSAID) class drug often used to relieve the inflammation, swelling, stiffness and joint pain. The mode of action of ACF is largely based on the inhibition of prostaglandin synthesis. ACF is a potent inhibitor of the enzyme cyclooxygenase (Cox), which is involved in the production of prostaglandins. *In-vitro* data indicate inhibition of Cox-1 and Cox-2 by ACF in whole blood assays, with selectivity for Cox-2 being evident [10]. Usually, elderly patient experience difficulty in swallowing tablet dosage form.

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Hence aim of the present study is to develop patient convenient effervescence tablet of ACF. Solubility of ACF can be enhanced by solid dispersion [11, 12] and secondly with effervescences dosage form. Effervescence tablet enhance the onset of action, bioavailability of ACF and also avoid first pass metabolism of ACF.

In the present study central composite design is used to optimize the effervescence tablets. A Box-Wilson Central Composite Design, commonly called 'a central composite design,' contains an imbedded factorial or fractional factorial design with center points that is augmented with a group of 'star points' that allow estimation of curvature. If the distance from the center of the design space to a factorial point is ± 1 unit for each factor, the distance from the center of the design space to a star point is $\pm \alpha$ with $|\alpha| > 1$. The precise value of α depends on certain properties desired for the design and on the number of factors involved [13].

MATERIAL AND METHODS:

Aceclofenac (ACF), anhydrous lactose and orange flavor were procured from Suvik Hitech Pvt. Ltd. (Gandhinagar, India). Anhydrous citric acid was gifted by ASES Chemicals, Jodhpur. Tartaric acid and sodium benzoate was purchased from Burgoyne Burbidges & Co. (Mumbai, India). Sucralose was gifted by Lincoln Pharma, Ahmedabad. Effersoda and mannitol was gifted by SPI Pharma, UK.

Investigation of Physicochemical Compatibility of Drug and Excipient

The physicochemical compatibility between ACF and excipients used in the tablets was studied by using differential scanning calorimetry (DSC- Shimadzu 60 with TDA trend line software, Shimadzu Co., Kyoto, Japan) and Fourier transform infrared (FTIR- 8300, Shimadzu Co., Kyoto, Japan) spectroscopy. [10]

In DSC analysis, the samples were weighed (5 mg), hermetically sealed in flat bottom aluminum pans, and

heated over a temperature range of 50 to 300°C at a constant increasing rate of 10°C/min in an atmosphere of nitrogen (50 mL/min). The thermograms obtained for ACF, excipient, and physical mixtures of ACF with excipients were compared. The infrared (IR) spectra were recorded using an FTIR by the KBr pellet method and spectra were recorded in the wavelength region between 4000 and 400 cm^{-1} . The spectra obtained for ACF, polymers, and physical mixtures of ACF with polymers were compared.[10]

Solubility enhancement of ACF by solid dispersion method

ACF has poor solubility in water and solid dispersion has been prepared to enhance solubility. Preliminary work was carried out for carrier screening using different carrier (β cyclodextrin, cross carmellose sodium, anhydrous lactose and PEG 6000) for preparation of solid dispersion by solvent evaporation method. The drug and carrier (1:1) was dissolved in dichloromethane and triturated in dry mortar until the solvent evaporated and a clear film of drug and carrier was obtained. Dispersions were pulverized using mortar and pestle and passed through a 250 μm sieve before packing in an airtight container. These solid dispersion formulations were optimized by evaluating % practical yield, % drug content & solubility in water. [14, 15]

Experimental Design

A central composite design was used in the present study to statistically optimize the formulation parameters and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the effervescence tablet formulations.

In this design two factors were evaluated, and experimental trials were performed at all 12 possible combination. The drug: carrier ratio (X_1) and the amount of effervescent Components (X_2) were selected as independent variables. Effervescent Time (Sec) (Y_1), Drug Release at 5 min. (Y_2) and Drug Release at 10 min. (Y_3) were selected as dependent variable.

Table 1: Variables in central composite design

Factors	Levels used, Actual (Coded)				
	-1.414	-1	0	1	1.414
Independent variables:					
X1 = Drug: Carrier Ratio	1: 0.79	1: 1	1: 1.5	1: 2	1: 2.2
X2 = Amount of effervescent Components (mg)	358.6	400	500	600	641.4
Constraints					
Dependent variable					
Y1= Effervescent time (sec)	45 sec to 75 sec				
Y2= Drug release at 5 minute	50 % to 60 %				
Y3= Drug release at 10 minute	60 % to 70 %				

In effervescent components, ratio of anhydrous citric acid: tartaric acid: effersoda should be fixed **1: 2: 4**.

Table 2: Composition of Aceclofenac Effervescent Tablet Batches

Ingredients	P1	P2	P3	P4	P5-P8	P9	P10	P11	P12
ACF	100	100	100	100	100	100	100	100	100
Anhydrous Lactose	100	79.3	100	150	150	150	200	220.7	200
Anhydrous Citric Acid	57.14	71.42	85.71	51.22	71.42	91.62	57.14	71.42	85.71
Tartaric Acid	114.28	142.84	171.42	102.45	142.84	183.24	114.28	142.84	171.42
Effersoda	228.58	285.74	342.87	204.91	285.74	366.54	228.58	285.74	342.87
Sodium Benzoate	30	30	30	30	30	30	30	30	30
Mannitol	900	820.7	700	891.4	750	608.6	800	679.3	600

The coded and actual values of the variables are given in Table 1. According to the CCD matrix generated by Design-Expert software (Trial Version 7.1.6, Stat-Ease Inc., MN), a total of 12 experiments, including four factorial points, four axial points and four replicated center points for statistical assessment the pure error sum of squares, were constructed. [16]

The non-linear computer generated quadratic model is given as

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

Where Y is the measured response associated with each factor level combination; b_0 is an intercept; b_1 to b_{22} are regression coefficients computed from the observed experimental values of Y; and X_1 and X_2 are the coded levels of independent variables. The terms $X_1 X_2$ and X_{ii} ($i = 1, 2$) represent the interaction and quadratic terms, respectively. The dependent and independent variables selected are shown in Table 1 along with their levels, which were selected based on the results from preliminary experimentation.

Formulation of ACF Effervescent Tablets

Direct compression method was used to prepare the effervescent tablets. For that all the excipients anhydrous citric acid, tartaric acid, effersoda, sodium benzoate, mannitol, sucralose & orange flavor with ACF : anhydrous lactose solid dispersion were mixed for 10 min and passed through sieve no. 72. Tablets were directly compressed using rotary tablet machine. Compositions of all the central composite batches are shown in Table 2.

Evaluation Parameters of Effervescent Tablet

The prepared ACF effervescent tablets were evaluated for diameter, thickness uniformity of weight, hardness, friability, drug content, effervescence time, effervescence lag time and *in vitro* dissolution studies. [17-20]

Diameter & Thickness

Diameter and thickness of tablets was important for uniformity of tablet size. Thickness was measured by using screw gauge on 3 randomly selected samples.

Hardness

The resistance of tablet for shipping or breakage, under conditions of storage, transportation and handling, before usage, depends on its hardness. The hardness of tablet of each formulation was measured by using Monsanto hardness tester and 3-5 kg/cm² is considered adequate for mechanical stability.

Friability

Friability is the measure of tablet strength. Roche Friabilator was used for testing the friability using the following procedure. Twenty tablets were weighed accurately and placed in the plastic chamber that revolves at 25 rpm for 4 minutes dropping the tablets through a distance of six inches with each revolution. After 100 revolutions the tablets were reweighed and the percentage loss in tablet weight was determined. Percentage friability

was calculated from the loss in weight as given in equation as below. The weight loss should not be more than 1%.

$$\% \text{ Friability} = \frac{\text{initial weight of tablets} - \text{final weight of tablets}}{\text{initial weight of tablets}} * 100$$

Drug Content

The drug content in each formulation was determined by 20 tablets and powder equivalent to 100 mg of Aceclofenac was transferred to 100ml volumetric flask and made the volume to mark with Methanol. The solution was filtered through a 0.45μ membrane filter, diluted suitably and the absorbance of resultant solution was measured spectrophotometrically at 273 nm using methanol as blank.

Effervescence Lag Time

Time period taken to start effervescence after tablet comes in contact with water was noted for 6 tablets.

Total Effervescence Time

It was carried out by placing one tablet in a 250 ml beaker containing water at 20° to 30°C numerous gas bubbles were evolved. This operation was repeated on further 5 tablets. The tablets comply with the test if each of the 6 tablets disintegrates in the manner prescribed within 3 minutes.

In Vitro Drug Release Study [21]

The dissolution experiment was performed using USP Apparatus 2 at 37± 2 °C with paddle speeds of 50 rpm in 900 ml dissolution medium (0.1 N HCl + 0.5 % SLS). A 5 ml sample was withdrawn at 5, 10, 20, 30, 40, 50 and 60 minutes and filtered through No. 41 Whatman filter paper. The same volume of fresh medium was replaced to maintain constant volume. The sample was suitably diluted and analyzed using UV-VIS spectrophotometer at 273 nm.

Stability Study

The promising formulation was subjected to short term stability study at 25°C/60% RH and 40°C/75% RH. Tablets were kept in polyethylene zip bag covered with aluminum foil. They were kept at 25°C/60% RH and 40°C/75% RH for 3 months and thereafter evaluated for appearance, diameter, thickness, hardness, friability, total effervescence time, assay and *in vitro* dissolution. Change in hardness, friability and drug content are probable effects anticipated during the stability study of such dosage forms.

RESULTS AND DISCUSSION:

Investigation of Physicochemical Compatibility of Drug and excipient

As shown in Figure 1 FTIR spectra of physical mixture of drug and excipient showed the same absorption peaks as that of the drug, illustrating absence of any interaction between ACF and used excipients. This behavior also supported by DSC spectra of ACF and ACF with excipient, which is shown in Figure 2. DSC spectra of pure ACF shows sharp characteristic endothermic peak at 155.00°C, corresponding to its melting temperature. This characteristic peak also observed in the drug excipient mixture, which

indicates no interaction between ACF and formulation excipient.

Table 3: Results of solid dispersion batches for carrier screening

Solid dispersion	% Yield	% Drug Content	Solubility in Water (mg/ml)
Pure ACF	-	-	0.28
ACF: Lactose anhydrous	93.57	97.26	0.94
ACF: B- cyclodextrin	94.36	96.88	0.72
ACF: Cross – carmellose	93.45	96.23	0.56
ACF: PEG 6000	94.58	95.26	

*Drug: carrier ratio is 1:1

Optimization of carriers for solid dispersion

Results of solid dispersion batches for carrier screening have shown in Table 3 reveal that solid dispersion of ACF with Lactose anhydrous as carrier shows comparatively maximum enhancement of drug solubility in water than solid dispersion with other carrier and hence this mixture was used in the preparation of tablet.

Results of physicochemical evaluation parameter of effervescent tablet

From the results of all batches of effervescent tablets, no significant change was observed in the evaluation parameters except effervescent time. Physical appearance and effervescence process is shown in Figure 3. Appearances of all tablets are accepted, along with its diameter and thickness. The diameter & thickness of all tablets were not variable, because the tablets were compressed from the same die so, no variation in the tablet diameter & thickness are expected. The hardness of all

batches are within the acceptance criteria between 3-5 kg/cm², which is sufficient for preventing the breaking of tablets in handling as well as during packing. Further hardness in this range allows easy disintegration of the tablet. The friability of all the batch are less than 1 (meeting the acceptance criteria), which prevents loss of material during handling. No significant change was observed in effervescent lag time also. All the batches pass in the test of uniformity of dispersion and assay for drug content. In vitro drug release profile of different formulation shows that more than 40 % drug is released in 5 min except batch P1, P2 and P4. In vitro drug release is satisfactory for fast onset of action of drug.

Results of Optimization of Formulation

The values of effervescent time, drug release at 5 min., drug release at 10 min. and drug content for all 12 batches are listed in Table 4. These responses are used to generate model equations for the three dependent variables. The model equations are validated by preparing and testing three new formulations. First, the estimated models for the response variables are discussed separately. Second, an optimum formulation is determined by a multivariate approach.

Statistical analysis of experimental data by Design-Expert Software

The results of the experimental design indicated that this system was influenced by the amount of effervescent agents and drug/carrier ratio which resulted in less effervescence time and fast drug release for the preparation of effervescent tablet.

Table 4: Observed responses in central composite design for Effervescent tablets:

Batch code	X ₁ (Drug: carrier)	X ₂ (Amount of effervescent component)	Y ₁ (Effervescent time)	Y ₂ (Drug release after 5 min)	Y ₃ (Drug release after 10 min.)	Drug Content (%)
P1	-1	-1	140	35.52	45.12	96.16
P2	-1.414	0	80	38.56	47.38	101.98
P3	-1	1	50	50.42	59.52	99.53
P4	0	-1.414	200	37.80	43.80	97.69
P5*	0	0	80	45.45	54.00	98.61
P6*	0	0	90	48.49	58.14	96.47
P7*	0	0	80	46.83	56.48	101.98
P8*	0	0	80	42.97	50.42	98.92
P9	0	1.414	40	56.76	67.24	101.68
P10	1	-1	150	43.80	50.97	98.61
P11	1.414	0	90	41.87	52.62	101.37
P12	1	1	50	51.52	60.90	98.30
A1	0.82	0.88	52	52.64	61.35	98.5
A2	0.54	0.90	48	54.28	63.19	98.9

Table 5: The quantitative factor effects and associated p value for the responses

Parameters	Y1 (Effervescence time)		Y2 (Drug release at 5 min.)		Y3 (Drug release at 10 min.)	
	Effect	P-value	Effect	P-value	Effect	P-value
X ₁	3.02	0.2667	1.76	0.0587	1.83	0.1147
X ₂	-52.03	<0.0001	6.24	0.0002	7.18	0.0004
X ₁ X ₂	-2.5	0.5002	-1.79	0.1436	-1.12	0.4562
X ₁ ²	0	1	-2.45	0.0274	-2.04	0.1158
X ₂ ²	17.5	0.0007	1	0.2813	0.72	0.5394

* Significant values at p < 0.05.

The best fit for each of the responses Y1, Y2, and Y3 were found for the quadratic models; compared to the linear model and the two-factor model the quadratic model had the largest r^2 values for all responses. Therefore the quadratic model incorporating interactional and quadratic terms was chosen to describe the effects of the variables. Each experimental response could be represented by the following quadratic of the response surface:

$$Y = b_0 + b_1 X_1 + b_2 X_2 + b_{12} X_1 X_2 + b_{11} X_1^2 + b_{22} X_2^2$$

In order to evaluate the significance of the quadratic models on the responses and their quantitative effects, analysis of variance (ANOVA) was carried out. Table 5 summarized the effects of the model terms and associated p values for all three responses. At a 95% confidence level, a model was considered significant if the p value < 0.05. The sign and value of the quantitative effect represent tendency and magnitude of the term's influence on the response, respectively. A positive value in the regression equation exhibits an effect that favors the optimization due to synergistic effect, while a negative value indicates an inverse relationship or antagonistic effect between the factor and the response [22]. Response surface analyses were also plotted in three-dimensional model graphs for optimization of tablets with suitable and satisfied physicochemical properties. The three-dimensional response surface plots for effervescence time, % drug release after 5 min. and % drug release after 10 min. were presented in Figure 5, 6 and 7, respectively. The response surface plots were used to describe the interaction and quadratic effects of two independent variables on the responses or dependent variables.

For all 12 formulations, the various factor combinations resulted in effervescence time of ACF vary from 40 sec to 200 sec. The results obtained in this design indicated that independent factors affecting effervescence time were the amount of effervescent components (X_2) and the quadratic term of effervescent components X_2^2 , with a p value of <0.05. Quantitative estimation of the significant models indicated that effervescent components had the prime influence on the effervescence time for its large negative coefficient (-52.03), suggesting that increasing the amount of effervescent components in the formulation decreased the effervescence time. The Y1 for all batches P1 to P12 showed good correlation co-efficient of 0.9879. The regression equation of the fitted model constructed for effervescence time was presented below:

$$Y_1 = 3.02 X_1 - 52.03 X_2 - 2.50 X_1 X_2 + 17.50 X_2^2 + 82.50$$

As expected, it was observed in Figure 3 that effervescence time could be decreased significantly with the increase in effervescent components amount, which might be related to the fact that more effervescence could be formed as the concentration of effervescent components increased which would provide sufficient fast onset of action.

Effect of formulation variable on Drug release at 5 minute (Y2) and 10 minute (Y3)

Concerning Y2 and Y3, the results of multiple linear regression analysis showed that both coefficients b_1 & b_2 have positive sign. The co-efficient value for X_1 and X_2 are 1.76 and 6.24 and those for Y3 are 1.83 and 7.18. The vales indicate that both factors affect drug release at 5 and 10 minute but X_2 has more effect on drug release than X_1 . Surface plot shows that as the concentration effervescent components increases drug release is increase drastically because solubility of drug can be increased by carbonated water, while drug to carrier ratio has optimum effect on drug release. The fitted equation relating the response Y2 and Y3 to the transformed factor is shown in following equation,

$$Y_2 = 1.76 X_1 + 6.24 X_2 - 1.79 X_1 X_2 - 2.45 X_1^2 + 1.00 X_2^2 + 45.94$$

$$Y_3 = 1.83 X_1 + 7.18 X_2 - 1.12 X_1 X_2 - 2.04 X_1^2 + 0.72 X_2^2 + 54.76$$

Optimization and validation:

Selection of best batch was carried out using Design Expert Software (Version 7.1.6, Stat-Ease Inc, and Minneapolis, MN). After statistical analysis the desirability function was applied to select the best batch. The desirable values selected for dependent variable Y1, Y2 & Y3 are given in Table 1. Desirable value range selected that was 5% vary from optimum value.

Table 6: Comparison of results of check point batch with theoretical value

Resp onses	A1		A2	
	Theoretical value	Practical value	Theoretical value	Practical value
Y ₁	50.90	52	50.28	48
Y ₂	50.70	52.64	51.71	54.28
Y ₃	60.97	61.35	61.65	63.19

Batch P12 came closest to satisfying all the selection criteria. The results were further reinstated using the overlay plot Figure 7. The yellow region of the plot indicates the area where all the selection criteria are satisfied. Batch P12 falls in this yellow area, indicating that formulation having drug: carrier ratio (1:2) and amount of effervescent components (600 mg) that possessed the desirable characteristics. So P12 batch was selected as optimized batch.

Two check point batches were formulated for the validation of the evolved model. Concentration of X_1 and X_2 and the observed response values are shows in the Table 6.

The result shows there are no significant difference between theoretical and experimental value of Effervescent time, % drug release at 5 min & % drug release at 10 min for both check point batches. So it can be concluded that this model was validated and fitted for this central composite design.

Result of Stability Study

Batch P12 having optimum concentration of sweetener and effervescent ingredients was subjected to short term stability study and the results after 3 months of stability

studies. The exposed tablets were evaluated for diameter, thickness, hardness, friability, effervescence lag time, total effervescence time, assay, dissolution and taste. All the parameters were within specifications. During stability of up to 3 months no significant changes were observed. From the stability data of tablets it was proved that optimized formulation is stable.

CONCLUSION:

The central composite design is demonstrated to be a useful method in the characterization of the effects of variables and process parameters in the development of an effervescent tablet formulation. Simple response surface models describing the influence of drug: carrier ratio and amount of effervescent components on effervescent time (sec), drug release at 5 min. and drug release at 10 min. are established and used to predict an optimum formulation given a minimum limit for the effervescent time and a maximum limit for the drug release. The predicted and the experimental data are found to be in good agreement. The work presented clearly demonstrates the usefulness of an experimental design approach for a fast and reliable formulation design.

REFERENCES:

1. Lindberg N, H.H., Encyclopedia of Pharmaceutical Technology. 3rd ed, ed. S. J.: Informa Healthcare.
2. Morle R, L.W., Plains M., Effervescent tablet, in Pharmaceutical Dosage form: Tablet, L.H. Lachman L, Schwatz J, Editor. 2005, Marcel Dekker. p. 285-86.
3. Ch.Prabhakar, K.B.K., A Review on Efferevesent Tablets. International Journal Of Pharmacy&Technology, 2011. 3(1): p. 704-712.
4. Rothhäuser, B., G. Kraus, and P.C. Schmidt, Optimization of an effervescent tablet formulation using a central composite design optimization of an effervescent tablet formulation containing spray dried l-leucine and polyethylene glycol 6000 as lubricants using a central composite design. European Journal of Pharmaceutics and Biopharmaceutics, 1998. 46(1): p. 85-94.
5. Jacob, S., A. Shirwaikar, and A. Nair, Preparation and evaluation of fast-disintegrating effervescent tablets of glibenclamide. Drug Dev Ind Pharm, 2009. 35(3): p. 321-8.
6. Krögel, I. and R. Bodmeier, Floating or pulsatile drug delivery systems based on coated effervescent cores. International Journal of Pharmaceutics, 1999. 187(2): p. 175-184.
7. Maximiano, F.P., et al., Development of effervescent tablets containing benzonidazole complexed with cyclodextrin. J Pharm Pharmacol, 2011. 63(6): p. 786-93.
8. Someshwar, K., et al., Formulation and evaluation of effervescent floating tablets of tizanidine hydrochloride. Acta Pharm, 2011. 61(2): p. 217-26.
9. Tadros, M.I., Controlled-release effervescent floating matrix tablets of ciprofloxacin hydrochloride: Development, optimization and in vitro-in vivo evaluation in healthy human volunteers. European Journal of Pharmaceutics and Biopharmaceutics, 2010. 74(2): p. 332-339.
10. Patel, R.P., et al., Formulation and evaluation of transdermal patch of aceclofenac. Research Journal of Pharmaceutical Dosage Forms and Technology, 2009. 1(2): p. 108-115.
11. Dhirendra, K., et al., Solid dispersions: a review. Pak J Pharm Sci, 2009. 22(2): p. 234-46.
12. Natarajan, R., et al., Dissolution enhancement of aceclofenac solid dispersion prepared with hydrophilic carriers by solvent evaporation method.
13. <http://www.itl.nist.gov/div898/handbook/pri/section3/pri335.htm>. [cited 2012 15/2/12].
14. Sunitha, N., Formulation and evaluation of aceclofenac solid dispersions for dissolution rate enhancement. International Journal of Pharmaceutical Sciences and Drug Research, 2010. 2: p. 146-150.
15. Gowthamarajan, K., et al., Dissolution enhancement of poorly soluble aceclofenac by solid dispersion technique and its comparison with marketed formulations. Int J Pharm Tech Res, 2010. 2(4): p. 2347-2356.
16. Gonzalez-Mira, E., et al., Optimizing flurbiprofen-loaded NLC by central composite factorial design for ocular delivery. Nanotechnology, 2011. 22(4): p. 045101.
17. The United States Pharmacopeia. 2005, United States Pharmacopoeial Convention: Rockville, MD.
18. European Pharmacopoeia, C.o. Europe, Editor. 2005, Strasbourg Cedex1, France,.
19. Indian Pharmacopoeia, G.o.I. Ministry of Health and Family Welfare, Editor. 2007, V: Delhi, India. p. 682-683.
20. British Pharmacopoeia. 2005, The Stationery Office, English: London.
21. Soni, T., et al., Development of discriminating method for dissolution of aceclofenac marketed formulations. Dissolution technologies, 2008. 15(2): p. 31.
22. Verma, S., et al., Quality by design approach to understand the process of nanosuspension preparation. International journal of pharmaceutics, 2009. 377(1): p. 185-198.