Formulation Design and Optimi ation of Sustained Release Tablets of Terbutaline Sulphate

Harish NM[1] *, Narayana Charyulu R[1], Shenoy KRP[3], Prabhu Prabhakara[1], Narendra C[2] and Nisha G Shetty[1].

[1]Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Paneer, Deralakatte, Mangalore-575 018.

[2] Department of Pharmaceutics, Krupanidhi College of Pharmacy, # 5 Sarjapur Road, Near Kudremukh Building, Koramangala, Bangalore 560 034, India.

[3] Astra Zeneca Pharma India Ltd, Hebbal, Bangalore

ABSTRACT

Submitted: 14/5/2010 Revised: 16/11/2010 Accepted: 9/4/2011

The sustained release matrix tablets of terbutaline Sulphate (TS) was prepared by wet granulation technique using polyvinyl chloride (PVC) and ethylcellulose. Citric acid was used to set up a system which would bring about gradual release of drug. In the present investigation, a 3^2 full factorial design was used to investigate the joint influence of 2 formulation variables: amount of PVC and Ethyl cellulose (EC). The granules were evaluated for angle of repose, bulk density, compressibility index, and drug content. The tablets were subjected to thickness, diameter, swelling index, weight variation test, drug content, hardness, friability, and *in vitro* release studies. The results of multiple linear regression analysis revealed that for obtaining a sustained dosage form, tablets should be prepared using an optimum concentration of PVC and EC. A contour plot is also presented to graphically represent the effect of the independent variables on the dissolution time carried out in phosphate buffer (pH 7.4) for 12 h. All the formulations exhibited Higuchi-dominated drug release. The mechanism of drug release was found to be anomalous.

Ke words: Sustained release tablets, Terbutaline Sulphate, polyvinyl chloride, Ethylcellulose, factorial design, contour plot.

INTRODUCTION

Terbutaline sulphate, an adrenergic agonist is an effective bronchodilator following oral administration[1,2]. Because of its short half-life of 3-4 h and low daily dose of 7.5 mg, TS could be formulated as a sustained release dosage form to impose patient compliance. Matrix tablet with different polymers is one of the methods used to modify the drug dosage form to retard the drug release rate[3]. Changing several formulation factors such as the type of excipients used and manufacturing process can alter the dug release from matrix tablets. Addition of non-polymeric excipients has shown to increase in the release rate of water soluble active principle. The increase in the release rate would be considerable with the water soluble excipients like lactose, citric acid, and tartaric acid[4]. Shufeng Nie et al., in their study showed that citric acid content and the pH of the medium could notably influence the dissolution behavior and mechanism of drug release[5].

***Address for Correspondence:**

Harish N M, Lecturer, Department of Pharmaceutics, NGSM Institute of Pharmaceutical Sciences, Paneer, Deralakatte, Mangalore-574 160, Karnataka, India.

E-mail : harishnayari@yahoo.co.in

The inert polymers such as PVC and ethyl cellulose were used for controlling the release of drug in the formulation of pharmaceutical dosage form. They are insoluble in water and digestive juices and also non-biodegradable. These polymers which do not swell even after contact with dissolution medium[6,7]. In this study, a central composite design with 3^2 factorial designs was employed with amounts of PVC (105.86-130mg/tablet) and EC (8.96-16.03mg/tablet) as independent variables and based on the results it was concluded that suitable combination of the two polymers along with citric acid provided the release of drug up to 12 h in a predermined manner.

MATERIALS AND METHODS

Materials

Terbutaline sulphate was a gift sample obtained from Astrazeneca Pharma India limited, Bangalore, India. Polyvinylchloride was purchased from sample from HydroPolymers, Sweden. Ethyl cellulose was obtained from Hercules incorporated, Wilmington, DE U.S.A. Citric acid anhydrous AR was obtained from SpectroChem Pvt Ltd, Mumbai, India, Stearyl alcohol was a sample from Lorol C18, Malaysia; Colloidal silica was a sample from Degussa,

Germany, Isopropyl alcohol was a sample from Shell Eastern Chemicals, Singapore.

Methods

Experimental Design:

Factorial design is an experimental design technique, by which the factors involved and their relative importance can be assessed. In the present study, the runs or formulations, which are designed, based on central component design with two factors at the orthogonal[8]. The optimization was done using Design Expert®, Stat ease, Version 6.0.

The two independent formulation variables evaluated include:

Factor A: Amount PVC X_1

Factor B: Amount of ethyl cellulose X_2

For simultaneous optimization each response must have a low and high value assigned to each goal. The values for actual and coded values are given in table 1.

Interaction Studies:

Drug polymer interaction studies were studied by DSC studies. The DSC analysis of pure drug, and drug loaded granules was carried out in the heating range of 40 °C to 300 °C at a rate of 10 °C /min^{-1} using TAG 1000 differential scanning colorimeter.

Calculation of Theoretical Release profile of TS from sustained-Release Formulations:

The total dose of TS for a twice-daily sustained-release formulation was calculated by the following equation[9] using available pharmacokinetic data;

$$D_t = \text{Dose } (1 + [0.693 \times t]/t_{1/2}).$$

Where, D_t = total dose of drug ; Dose = dose of the immediate release part (2.5 mg) ;

t = time (h) during which the sustained release is desired (24 h) ; t1/2 = half-life of the drug.

$$Dt = 2.5\ (1 + (0.693 \times 12) / 4.12) = 7.5 \text{ mg}.$$

The formulation therefore should release 2.5 mg in the first hour like conventional tablets, and release 0.45 mg of the drug per hour up to 12 h. Based on this release profile the matrix made up of inert polymer in study is expected to show the desired release profile until 12 hrs which will comply with theoretical drug release, so as to meet the therapeutic goal. The release profile at the end of 1st h, 2nd h, 4th h, 6th h and 12th h should be between 17-32%, 30-55%, 50-75%, 65-86% and >82% respectively.

Amount of PVC was chosen as factor A because of its robust and inert nature of the polymer, which helps maintain the shape during the dissolution process. Central composite design (CCD) was considered, according to the model. Totally 12 experiments were conducted with three replicates of center point.

The factor B was expected to bind the tablet & also participate in the matrix formulation. Ethyl cellulose was chosen as a polymer because of its inert, stable and good binding property. Amount of PVC is studied at three levels as 110, 120, 130. Three levels of Ethyl cellulose 10, 12.50, and 15 were used in the study. The composition of various formulation taken for the present study is shown in table 2.

Preparation of Compressed Matrices:

Different tablet formulations were prepared by wet

Table 1: Actual and coded values of the factors

Model	Actual values			Coded values		
Factor	**Low level**	**Mid level**	**High level**	**Low**	**Mid**	**High**
Factor-A	110mg	120mg	130mg	-1	0	+1
Factor-B	10	12.5	15	-1	0	+1

Table 2: Composition of various formulation

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Terbutaline Sulphate	5	5	5	5	5	5	5	5	5	5	5	5
PVC	110	130	110	130	105.86	134.14	120	120	120	120	120	130
Ethyl Cellulose	10	10	15	15	12.5	12.5	8.96	16.03	12.5	12.5	12.5	14.6
Citric Acid	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9	6.9
Stearyl Alcohol	9	9	9	9	9	9	9	9	9	9	9	9
Colloidal Silica	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45	3.45
IPA	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s	q.s
Colloidal Silica	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5

granulation technique with different ratios of PVC and EC with the composition as given in table 1. All the ingredients were passed through sieve number 60. Weighed quantities of drug and polymers were mixed thoroughly and a sufficient volume of granulating agent (solution of ethyl cellulose in isopropyl alcohol) was added slowly. After enough cohesiveness was obtained, the mass was passed through 22/44 mesh. The granules thus obtained were dried at 50 °C for 6 h in hot air oven (Rotek, Kerala, India) and thereafter kept in a desiccator for 12 h at room temperature. After drying, the granules retained on sieve number 44 were mixed with 15% of fines (granules that passed through 44 mesh). Colloidal silica was finally added as a glidant. The practical weight of tablet was calculated based on the drug content of the granulations and the granules were compressed in to tablets by biconvex punches of 7 mm diameter using a 16-Station tablet compression machine (RIMEK, India, Minipress II).

Evaluation of granules:

a) Angle of Repose:

The angle of repose of granules was determined by the funnel method. The accurately weighed granules were taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the granules. The granules were allowed to flow through the funnel freely onto the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation[10]:

$$\tan\theta = h/r \quad \text{----------} \quad (1)$$

Where *h* and *r* are the height and radius of the powder cone.

b) Bulk Density

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder using DBK digital bulk density apparatus. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from a height of 2.5 cm at 2-second intervals. The tapping was continued until no further change in volume was noted. LBD and TBD were calculated using the following formulas[11].

LBD = weight of the powder/volume of the packing ----------(2)

TBD = weight of the powder/tapped volume of the packing ----------(3)

c) Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index[11]:

Carr's index (%) = [(TBD – LBD) × 100]/TBD ----------(4)

Evaluation of Tablet Properties

a) Thickness: The thickness of the tablets was determined using a thickness Digital caliper gauge (Mitutoyo, New Delhi, India). Five tablets from each batch were used, and average values were calculated[11].

b) Weight Variation Test: To study weight variation, 20 tablets of each formulation were weighed using an electronic balance (Mettler AE 163), and the test was performed according to the official method given in BP.

c) Drug Content: Five tablets were weighed individually and the drug was extracted in 0.005N sulphuric acid. The method was developed in house for estimation of TS in tablet. The drug content was determined by High performance liquid chromatography (HPLC) on a column with octadecylsilane as a stationary phase.

d) Hardness and Friability: For each formulation, the hardness and friability of 6 tablets were determined using the Monsanto hardness tester and the Roche friabilator (Campbell Electronics, Mumbai, India), respectively.

e) Swelling studies: Swelling studies were carried out in order to investigate whether, the extent of swelling varied for the different formulations. When a matrix comes in contact with an aqueous solution, wetting occurs, first at the surface and then proceeding into the matrix through microscopic pores. The nature of polymer plays an important role in this swelling process of the matrix tablets. Three metallic baskets containing a matrix tablet of each formulation were weighed and placed in 1000ml of phosphate buffer (pH 7.4) at 37.0 $\pm$ 0.5 ^{0}C. At hourly interval, the previously weighed baskets with the tablet were removed, gently wiped with a tissue to remove surface water, re-weighed and then placed back into the vessel as quickly as possible. Then mean weights were determined for each formulations and degree of swelling(s) was calculated according to the relationship[12].

$$S = (W_s - W_d / W_d) \times 100$$

Where W_d and W_s are the drug and swollen matrix weights, respectively at immersion time t in the buffer, the swelling degree was the mean value of three measurements.

***In vitro* release studies:**

Dissolution studies were carried out in 900 ml of dissolution medium (pH 7.4 buffer) using USP 23 dissolution apparatus II at 37 ^{0}C ± 2 °C and 50 rpm. Samples (5.0 ml) were withdrawn at 1st h, 2nd h, 4th h, 6th h and 12th h. The samples were filtered and analyzed using HPLC ion-pair chromatography on a column with octadecylsilane as stationary phase at a

wavelength of 280 nm. An equal volume of fresh medium was replaced to maintain sink condition. To know the mechanism of drug release from these formulations, the data were treated according to zero order (cumulative amount of drug released vs time) pattern, first-order (log cumulative percentage of drug remaining vs time), Higuchi's[15] (cumulative percentage of drug released vs square root of time), and Korsmeyer et al's[16] (log cumulative percentage of drug released vs log time) equations.

RESULTS AND DISCUSSION

Formulations were prepared randomly following central component design for the formulation using PVC & EC. An ideal extended release formulation should release the drug at least for 12 h[11,13]. Hence an inert polymer mixture of PVC and EC were used to form the matrix in which the drug was homogeneously dispersed. Citric acid used in the formulation acts like a channeling agent for the drug to diffuse into the aqueous medium. The DSC curves of pure drug in comparison with drug loaded granules showed in figure 1. It was evident from the DSC profile that the pure TS exhibited a sharp endothermic peak at 263 ^{0}C which corresponds to the melting point of the drug. The DSC profile of drug loaded granules showed a peak at the temperature corresponding to TS melting point but with the loss of its sharp appearance. The decrease in the intensity of the peak may be due to the presence of other substances particularly low melting point citric acid and stearyl alcohol which could have solubilized the drug.

Granulation is an important process in the production of many dosage forms involving the sustained release of a drug from coated or matrix-type particles. Physical properties of granules such as specific surface area, shape, hardness, surface characteristics, and size can significantly affect the rate of dissolution of drugs contained in a heterogeneous formulation. The granules of different formulations were evaluated for angle of repose, LBD, TBD, compressibility index, total porosity, and drug content (Table 3). The results of angle of repose and compressibility index (%) ranged from 21.20 ± 0.02 to 29.85 ± 0.02, and 11.25 ± 0.03 to 13.75 ± 0.02, respectively. The results of LBD and TBD ranged from 0.283 ± 0.03 to 0.512 ± 0.04 and 0.325 ± 0.06 to 0.582 ± 0.04, respectively. The results of percentage porosity of the granules ranged from 26.92 ± 0.03 to 37.61 ± 0.04. The drug content in a weighed amount of granules of all formulations ranged from 95.53 ± 0.04 to 98.55 ± 0.03% which were within the acceptable limits.

Drug content and physical evaluation:

The assayed content of the drug in various formulations varied between 98.87 to 99.08%. The thickness of the tablets ranged from 3.34 to 3.45 ± 0.04 mm. The average percentage deviation of 20 tablets of each formula was less than ± 5%. Drug content was found to be uniform among different batches of the tablets and ranged from 97.53 ± 0.03 to 100.34 ± 0.05. The hardness and percentage friability of the tablets of all batches ranged from 4 ± 0.13 to 5 ± 0.42 kg/cm^2 and 0.39 ± 0.02 to 0.854 ± 0.05%, respectively (Table 4). It was found that as the amount of EC increased showed decrease in friability and increase in hardness. Whereas in case of PVC there was increase of hardness with gradual increase in PVC up to 120 mg. Further increase did not have any profound effect on the harness of the tablet. All the tablet formulations showed acceptable pharmacotechnical properties and complied with the in house specifications for weight variation, drug content, hardness, and friability.

Table 3: Properties of granules studied to understand the flow property

FORMULA	Precompression parameters			
	Bulk Density* (g/cc)	Tapped density* (g/cc)	Carr's index* (%)	Angle of repose* (ø)
F1	0.463±0.02	0.5291±0.06	14.2±0.02	22.1±0.04
F2	0.4575±0.03	0.5382±0.01	14.45±0.01	25.66±0.02
F3	0.466±0.05	0.505±0.02	8.36±0.02	23.99±0.03
F4	0.525±0.01	0.669±0.06	16.34±0.06	21.99±0.01
F5	0.501±0.03	0.648±0.01	15.67±0.03	24.65±0.05
F6	0.45±0.05	0.575±0.03	12.22±0.01	28.97±0.03
F7	0.45±0.01	0.55±0.07	18±0.04	24.84±0.05
F8	0.43±0.05	0.52±0.02	18.22±0.03	24.89±0.03
F9	0.53±0.02	0.58±0.02	8.16±0.01	20.34±0.02
F10	0.525±0.01	0.669±0.06	16.34±0.06	21.99±0.01
F11	0.501±0.03	0.648±0.01	15.67±0.03	24.65±0.05
F12	0.45±0.05	0.575±0.03	12.22±0.01	28.97±0.03

* All values are expressed as mean ± SE, n = 5.

***In vitro* dissolution release studies:**

Release data of TS from matrices containing various citric acid concentrations produced straight-line plots with the regressions were calculated for drug release for a time up to 12h. The correlation coefficients for most of data were 0.9987 and other regression parameters for all curves in phosphate buffer pH 7.4. The theoretical release profile is important to evaluate with respect to release rates and to ascertain whether it releases the drug in a predetermined manner. These results indicated matrices processing a greater proportion of citric acid exhibited a drug release closer to a diffusion-controlled process and could release a higher amount of drug. Hence to control the drug release the amount of citric acid in the formulation was optimized at 6.5mg/tablet. *In vitro* dissolution study was performed on 12 formulations to chart the dissolution profile in order to obtain a release profile which was found to be very close to the predicted release profile. The protected release profile is based on the minimum amount of drug required to show therapeutic effects in the body for an oral dose 7.5 mg. Table 5, shows that release for a period of 12 h varies in a nearly linear descending pattern with decrease in the amount of PVC and EC. During the *in vitro* dissolution test, the porosity and the thickness of

Fig. 1: A differential scanning calorimetric scan DSC thermograms of (A) Pure terbutaline sulphate (B) Drug- loaded granules. (C) Blank granules.

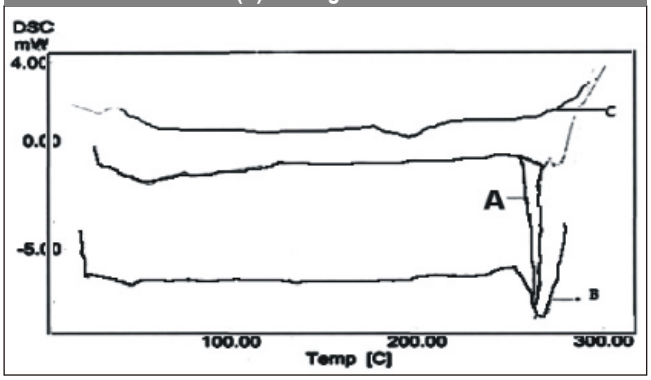


Table 4: Data of Post Compression evaluation parameters of various formulations

Formulation Code	Friability (%)	Hardness kg/cm^2	Tablet Weight mg	Thickness mm (%)	Drug Content	Swelling Index at 12h(%)
F1	0.39	4	145.85	4.22±0.77	99.12	-0.43
F2	0.566	4.5	165.85	4.32±0.35	98.56	-0.44
F3	0.766	4	150.85	4.38±0.57	101.34	-0.43
F4	0.342	5	170.85	4.44±0.39	100.46	-0.45
F5	0.289	4	144.21	4.12±0.75	99.63	-0.45
F6	0.154	5	172.49	4.1±0.68	97.53	-0.43
F7	0.436	4.5	154.81	4.32±0.38	100.98	-0.43
F8	0.478	4.5	161.88	4.28±0.35	99.86	-0.45
F9	0.529	4	158.35	4.12±0.57	100.45	-0.44
F10	0.683	4.5	158.35	4.32±0.35	100.06	-0.47
F11	0.635	5	158.35	4.38±0.77	98.12	-0.42
F12	0.212	5	170.45	4.44±0.3	100	-0.44

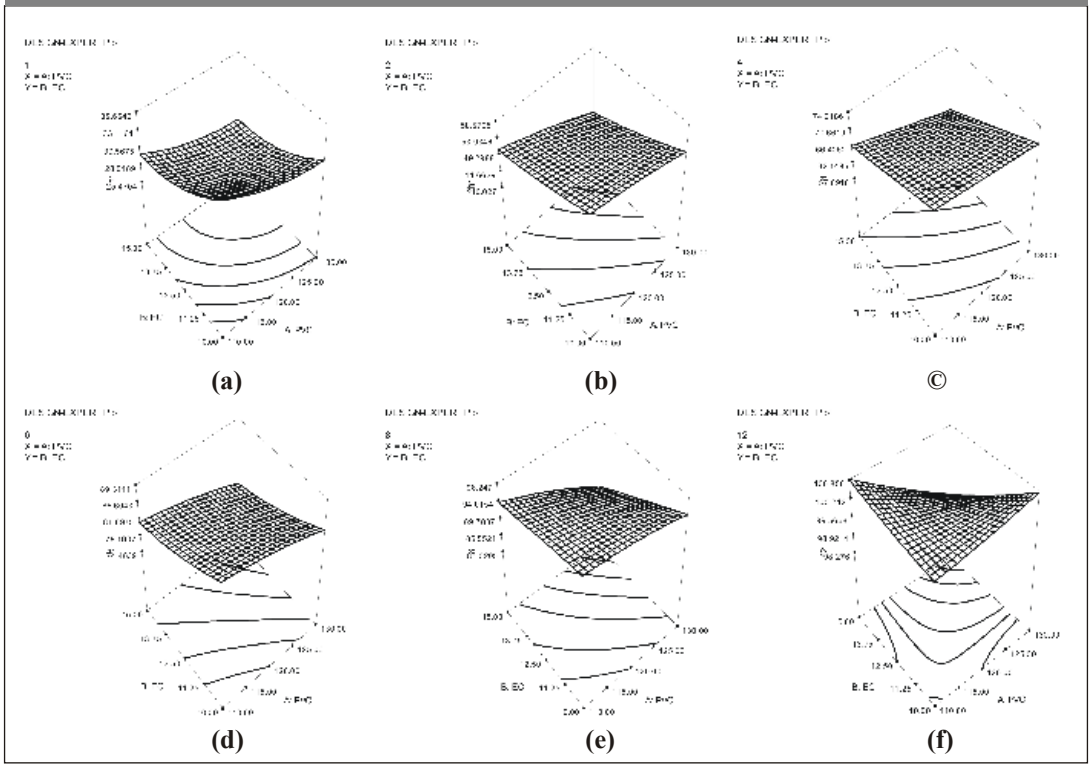
Table 5: Design and Summary Response Data.

STD	Run	Type	PVC	EC	1h	2h	4h	6h	8h	12h
1	3	Fact	110	10	36.34	59.15	72.76	89.56	99.13	100.1
2	1	Fact	130	10	30.73	49.89	66.98	80.89	92.45	100.6
3	4	Fact	110	15	30.1	52.3	70.5	81.7	95.7	100.5
4	2	Fact	130	15	25.32	39.96	60.45	72.98	80.89	97.79
5	6	Axial	105.86	12.5	32.34	53.98	69.77	84.12	95.12	100.9
6	10	Axial	134.14	12.5	26.8	43.3	62.8	77.6	86.8	99.7
7		7Axial	120	8.96	34.5	58.3	80.1	90.2	99.1	100.8
8	11	Axial	120	16.03	26.89	43.67	56.32	78.23	85.34	99.87
9	9	Center	120	12.5	28.12	51.65	67.8	81.76	93.98	99.86
10	8	Center	120	12.5	26.13	48.66	65.76	80.65	93.56	99.76
11	5	Center	120	12.5	29.34	49.85	68.96	82.31	90.54	100.1

Table 6: Kinetic models of various formulations

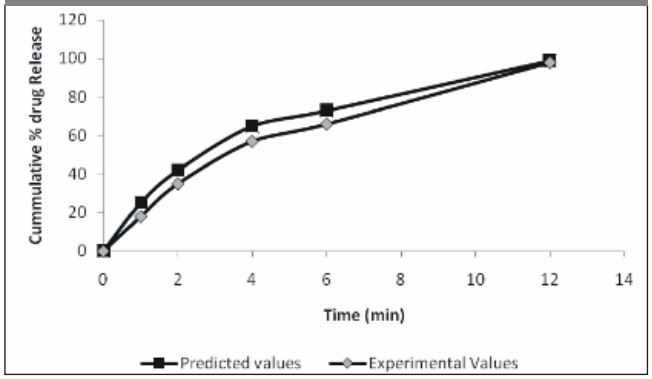
Formulation	First order plots	Zero order plots.	Korsmeyer et.al., plot		Higuchi
	R^2	R^2	n	R^2	R^2
F1	0.9985	0.8728	0.5803	0.9976	0.9974
F2	0.9966	0.8389	0.5821	0.9404	0.9395
F3	0.9617	0.8096	0.5126	0.9754	0.9749
F4	0.9508	0.8893	0.5961	0.9915	0.9833
F5	0.9857	0.8591	0.652	0.9923	0.9865
F6	0.9876	0.8632	0.634	0.9987	0.9952
F7	0.9753	0.8331	0.724	0.9945	0.9823
F8	0.9834	0.8111	0.641	0.9845	0.9872
F9	0.9975	0.8345	0.662	0.9423	0.9241
F10	0.9965	0.8341	0.645	0.9786	0.9843
F11	0.9871	0.7823	0.712	0.9872	0.9832
F12	0.9952	0.8123	0.722	0.9833	0.9845

Fig. 2: 3D Graph of response of dissolution profile for different ratios of PVC: Ethyl cellulose (a) 1st hour (b) 2nd hour (c) 4th hour (d) 6th hour (e) 12th hour.



depletion zone became greater after citric acid was lost from matrices gradually, which consequently induced the drug to diffuse from the matrix more easily through the pores created by loss of citric acid. Similar observation were seen by Shufeng Nie et al., using HPMC matrices[5]. The effect of different ratios of PVC and EC are shown in figure 2 depicting its effect on release of the drug at different time intervals. Incorporation of a high concentration of PVC and EC sustained the drug release in a better manner, which could be attributed to the decreased penetration of the solvent molecules in the presence of hydrophobic polymer, leading to decreased diffusion of the drug from the matrix. Based on this optimized formula was calculated which is as follows TS 7.5 mg, PVC 120 mg, EC 16.03 mg, citric acid 6.5mg, stearyl alcohol 9mg and colloidal silica 1.5mg. The predicted values given by the software and observed results from the optimized tablet formulation illustrate that the proposed model has good predictive ability (Fig 3). The model terms for the 'n' was

Fig. 3: Dissolution profile of optimum formulation and predicted formulation



found to be significant F value and high regression value (0.9889) indicated adequate fitting of the quadratic model. It was found that with increase in polymer ration the release decreased showing variation in predicted release. The interaction terms can be studied further with the help of 3D Graph response of dissolution profile for different ratios of PVC is shown in figure 1. When the date was plotted according to the first order equation, the formulations showed a fair linearity, with regression values between 0.926 and 0.9973. Release of the drug from a matrix tablet containing hydrophilic additives such as citric acid suspended in a hydrophobic matrix results from the pore formed due to loss of water soluble constituent. Diffusion of the drug from the dosage matrix into the *in vitro* study fluid depends on the concentration gradient. As gradient varies, the drug diffuses at a comparatively slower as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics. The release kinetics applied for different equations are shown in table 6. In our experiments, the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity (R^2:0.9974 to 0.9241), with slope (*n*) values ranging from 0.5126 to 0.724, indicating that the release mechanism appears to be coupling of diffusion and erosion mechanisms so called anomalous diffusion. The relative complexity of this formulation and its components may indicate that the drug release is controlled by more than one process. Similar results were reported by Raghuram Reddy K et al., using eudragit polymers.

CONCLUSION

The results of 3^2 full factorial design revealed that the amount of PVC and EC significantly affect the dependent variables, disintegration time, and percentage friability.

It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

REFERENCES

1. Rang and Dale., HP. Rang., MM Dale., JM.Ritter., P.K. Moore., In; Text book of clinical pharmacology, 5th Ed,Churchill Livingstone, 2003; pp 346.
2. Christopher Haslett., Edmin R Chilvers, Nicholas and Boon, Nicki R Colledge, In; Principles and Practice of Medicine "Davidson's", 19th Ed, Churchill Livingstone,2002, pp 513.
3. Lordi GN. Sustained release dosage forms. In; Lachman L, Liberman HA,Kanig JL, Eds. The Theory and Practice of Industrial Pharmacy, Varghese Publishing House, Mumbai, India, 1987, pp 430.
4. Rogelio Espinoza., Enrique Hong., Leopoldo Villafuerte., Influence of ad mixer citric acid on the release profile of pelanserin hydrochloride from HPMC matrix tablets, Int J pharm**,** 2000; 201: 165-174.
5. Shu Fang N, Weisan P, Xiaodong Li, and Xueming Wu, The effect of citric acid added to HPMC matrix tablets on the Release profile of Vinpocetine, Drug Dev Ind Pharm, 2004; 30(6): 627-635.
6. Kaisri U, Padungkwan C, and Sukavat A, Influence of Process Variables on Physical Properties of the Pellets Using Extruder and Spheronizer Drug Dev Ind Pharm**,** 1999; 25: 46-61 .
7. Luigi GM, Coles M, Gravell K, Stephenson S, and Thomson CM, The use of a hydrophobic Matrix for the sustained Release of a Highly Soluble drug, Drug Dev Ind Pharm 2000;26(1): 79-83.
8. Jesusa Joyce N. Optimization of a new filler/binder for direct compression using central composite design. Drug Dev Ind Pharm 1997; 23: 945-950.
9. Rawlins EA. Bentley's Text Book of Pharmaceutics. 8th Ed, London, England: Cassell and Collier MacMillan; 1977.pp 658-666.
10. Cooper J, Gunn C. Powder flow and compaction. In: Carter SJ, eds. *Tutorial Pharmacy*. New Delhi, India: CBS Publishers and Distributors; 1986:211-233.
11. Raghuram Reddy K, Srinivas Mutalik and Srinivas Reddy, Once-Daily sustained release matrix tablets of nicorandil: Formulation and *in vitro* evaluation. AAPS Pharm Sci Tech**,** 2003; 4: Article 61 (http://www.aapspharmscitech.org). cited on 23/01/2010.
12. Machida, H.; Masuda, H.; Fujiyama, N.; Ito, S.; Iwata, M.; Nagai, T. Preparation and Phase II Clinical Examination of Topical Dosage Form for Treatment of

Car-cinoma Colli Containing Bleomycin with Hydroxy Propyl Cellulose. Chem. Pharm. Bull. 1979, 29, 93-100.

13. Chong-Kook Kim, Mi-Jung Kim, Kyoung-Hee Oh, Preparation and evaluation of sustained release microspheres of Terbutaline Sulphate, Int J Pharm, 1994; 106: 213-219.

14. Pao-Chu Wu, Yaw-Bin Huang, Jui- sheng Chang, Ming-Jun Tsai, Yi-Hung Tsai. Design and Evaluation of sustained release microspheres of Potassium chloride prepared by Eudragit, Euro J Pharm Sci**.,** 2003;19: 115-122.

15. Higuchi T. Mechanism of sustained action medication. Theoretical analysis of rate release of solid drugs dispersed in solid matrices. J Pharm Sci., 1963; 52: 1145-1149.

16. Korsemeyer RW, Gurny R and Peppas NA. Mechanisms of solute release from porous hydrophilic polymers Int J Pharm, 1983; 15: 25-35.

****