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Formulation Optimization of Isoxsuprine HCl Sustained Release Tablet Using Full Factorial Design

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ABSTRACT

Isoxsuprine hydrochloride, a β_2 agonist used in peripheral vascular disease was formulated into sustain release matrix tablets, by wet granulation method using HPMC K15M as release retardant in different proportions and PVP K25 as a binder. The parameter optimized using 3^2 factorial designs. The tablets of all batches were evaluated for drug content, hardness, friability, weight variation and in vitro drug release profile. The dissolution profiles of formulated tablets were compared with a marketed product. The similarity factor (f_2) was calculated to check the similarity with marketed product. Different dissolution models were applied to drug release data in order to evaluate release mechanisms and kinetics. Mathematical treatment of the *in vitro* drug release data suggests that, the drug release of all the formulations exhibited nearly zero-order kinetics, the release exponent n ranged from 0.69 to 0.8 indicate that drug release from the all batches occurred by non-Fickian diffusion mechanism (anomalous transport), i.e. the release is ruled by both diffusion of the drug and dissolution of the polymer. According to SUPAC guidelines the formulation containing combination of 25% HPMC K15M and 10% PVP K25 is the most similar formulation to marketed product.

Keywords: Isoxsuprine HCl, factorial design, release kinetics, sustained release

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INTRODUCTION:

Drug delivery in conventional dosage forms often suffers from the drawbacks of repeated drug administration and large fluctuations in drug blood levels. The frequency with which a rapidly absorbed and distributed drug must be given in a conventional dosage form is dependent upon intrinsic properties of the drug, viz. elimination half-life ($t_{1/2}$).[1]

Sustained release dosage forms are designed to complement the pharmaceutical activity of the medicament in order to achieve better selectivity and longer duration of action including improved therapeutic effect, increased patient compliance by reducing dosing frequency and decrease in incidence and /or intensity of adverse effect by a constant blood concentration.[2] Isoxsuprine hydrochloride, a β_2 agonist used as a vasodilator in peripheral vascular disease.[3] This drug has a shorter biological half life about 2.5 to 3 hour make it ideal to prepare sustained release tablet.

Sustained release matrix tablet is relatively easy to fabricate by incorporating drug molecules into a matrix in slowly disintegrating or inert porous material containing a hydrophilic rate controlling polymer.[4, 5, 6] Matrix systems are widely used in oral controlled drug delivery because of their flexibility (which results in obtaining desirable drug release profile), cost effectiveness and broad regulatory acceptance[3, 7]. Cellulose ethers such as hydroxypropyl cellulose(HPC), hydroxypropyl methylcellulose (HPMC) and sodium carboxymethylcellulose (NaCMC), copolymers of acrylic-methacrylic acid (Eudragits) such as Eudragit RL and RS and some natural gums like Guar Gum and xanthan gum are widely used hydrophilic polymers as release retardant.[3, 8] Hydroxypropyl methylcellulose has been used as matrix former for controlled release of naproxen.[9]

So the purpose of this research was to prepare sustained release tablet of isoxsuprine HCl using hydroxypropyl methyl cellulose (HPMC) K15M and PVP K25 by wet granulation method and applied the different dissolution model to study the drug release mechanisms and kinetics. A 3^2 full factorial design was employed to investigate the effect of two independent variables (factors), i.e. The amounts of HPMC K15M and PVP K25 on the dependent variables, i.e. Q_1, Q_8, $T_{50\%}$ (% drug release after 1, 8,hours and time required to release 50% drug respectively).

MATERIALS AND METHODS

Materials

Isoxsuprine HCl was received as a gift sample from Corel Pharma Chem, ahmedabad. HPMC K15M, PVP K25 and MCC were received as a gift sample from Torrent research center,

Gandhinagar, India. All other materials and chemicals used were of either pharmaceutical or analytical grade.

Methods

Preparation of tablets

Tablets were prepared by wet granulation method. Drug, HPMC K15M, PVP K25 and MCC were passed through 60# sieve and mixed in porcelain dish. Dump mass was prepared using the isopropyl alcohol and these mass was passed from 20# sieve to form granules. The resulted granules were dried at room temperature and passed through 20# sieve and retained on 40# sieve. Retained granules were collected and added 10% fine to it. 1% magnesium stearate and 2% talc was added at last and mixed it. The powder mixer was compressed in 8 mm diameter flat punches using a multi punch tablet compression machine (Cad mach, Ahmadabad, India).

Evaluation of tablets

All prepared matrix tablets were evaluated for uniformity of weight[10] and assay[11] as per I.P. method. Friability was determined using Roche friabilator. Hardness was measured by using Pfizer hardness tester.[12]

***In vitro* dissolution studies**

The *in vitro* dissolution study of isoxsuprine HCl tablets was performed using USP apparatus type II(model TDT-08T, Electrolab, Mumbai, India) with agitation speed of 75 rpm at 37^0C ± 0.5^0C using distilled (900 mL) as a dissolution medium. At the predetermined time intervals, 10-mL samples were withdrawn, filtered through a 0.45μm membrane filter and assayed at 269 nm using Shimadzu-UV1800 double-beam spectrophotometer (Shimadzu, Kyoto Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve.

Optimization of variables using 3^2 randomized full factorial designs

A 3^2 randomized full factorial design was used in the present study. In this design 2 factors were evaluated, each at 3 levels, and experimental trials were performed for all 9 possible combinations. The amounts of HPMC K15M (X1) and PVP K25 (X2) were selected as independent variables in 3^2 full factorial design, while Q_1, Q8 and $T_{50\%}$ (% drug release after 1, 8,hours and time required to release 50% drug respectively) were taken as dependent variables. The formulation layout for the factorial design batches (F_1-F_9) is shown in Table 1.

Drug release kinetics study

The dissolution profile of all batches were fitted to various models such as zero order, first order[13], Higuchi[14], Hixon Crowell[15], Korsemeyer and Peppas[16] to ascertain the kinetic of drug

release. The method described by Korsemeyer and Peppas was used to describe mechanism of drug release.

Table 1: 3^2 Full Factorial Design Layouts

Batch Code	Variable level in coded form		Q_1	Q_8	$T_{50\%}$	f_2
	X_1(%)	X_2 (%)				
F-1	-1	-1	9.33	56.64	6.92	80.24
F-2	-1	0	12.24	56.4	6.93	76.67
F-3	-1	1	8.37	43.94	7.1	53.65
F-4	0	-1	12.89	55.57	9.33	76.24
F-5	0	0	11.27	56.36	6.9	93.02
F-6	0	1	8.7	45.61	7.02	56.28
F-7	1	-1	20.28	86.25	9.03	32.84
F-8	1	0	18.99	85.24	2.98	32.89
F-9	1	1	8.7	46.95	3.15	60.88
Coded Values	**Actual Values**					
	X_1 (%)			**X_2 (%)**		
-1	20			5		
0	25			10		
1	30			15		

- X_1 and X_2 indicates the amount of HPMC K15M and PVP K25 respectively.
- Q_1, Q_8 and $T_{50\%}$ percentage drug release after 1 and 8 hour and time required for 50% drug release, respectively.
- Total weight of tablet 200 mg of each containing 20% Isoxsuprine HCl, 2% talc and 1% magnesium stearate and MCC up to quantity sufficient.

Comparison of dissolution profiles for selection of optimum batch

The similarity factor (f_2) given by SUPAC guidelines for a modified release dosage form was used as a basis to compare dissolution profiles. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profile of products were compared using a f_2 which is calculated from following formula,

$$f_2 = 50 X \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} x\,100\right\} \qquad (1)$$

Where, n is the dissolution time and R_t and T_t are the reference (here this is the dissolution profile of marketed product) and test dissolution value at time t.[17]

RESULTS AND DISCUSSION

Physical Evaluation

The physical appearance, tablet hardness, friability, weight variation, and drug content uniformity of all tablet formulations were found to be satisfactory and reproducible as observed from the data in Table 2. Tablet hardness was found to be good (4.8 ± 1.00 to 5.6 ± 1.50 kg/cm^2)

depending on the compression force applied. In the present study, the percentage friability for all the formulations was found below 1% indicating that friability (%) is within the acceptable limits. In a weight variation test, the pharmacopoeia limit for the percentage deviation for tablets of between 80 mg to 250 mg is ±7.5%. The average percentage deviation of all tablet formulations was found to be within above limit, and hence all formulations passed the test for uniformity of weight as per official requirement. Good uniformity in drug content was found among different batches of the tablets.

Table 2: Results of factorial design batches (F_1-F_9)

Batch	Assay (%) (n=10)	Friability (%) (n=10)	Hardness (Kg/cm^2) (n=10)	Average Weight(mg) (n=20)
F-1	97.62	0.27	5.4 ± 0.60	197.74 ± 2.81
F-2	101.3	0.42	4.8 ± 1.00	201.45 ± 2.65
F-3	99.7	0.31	5.1 ± 0.50	204.09 ± 2.00
F-4	99.52	0.38	5.3 ± 1.20	198.62 ± 3.50
F-5	101.1	0.20	4.9 ± 0.89	204.23 ± 2.00
F-6	98.08	0.26	5.4 ± 0.55	197.30 ± 2.74
F-7	99.74	0.38	5.3 ± 0.98	196.60 ± 1.15
F-8	98.23	0.37	5.2 ± 1.20	198.57 ± 2.54
F-9	100.6	0.15	5.6 ± 1.50	204.03 ± 2.23

Full factorial design

A statistical model incorporating interactive and poly nominal terms was used to evaluate the responses.

$Y= b_0 + b_1X_1 + b_2X_2 + b_3X_1X_2 + b_4X_1^2 + b_5X_2^2$

Where, b_0 is the intercept representing the arithmetic average of quantitative out come of 9 runs b_1 to b_8 are the coefficient computed from the observed experimental value of Y & X_1, X_2 are the coded level of the independent variable.

Where Y is the dependent variable, b_0 is the arithmetic mean response of the 9 runs, and b_1 is the estimated coefficient for the factor X_1. The main effects (X_1 and X_2) represent the average result of changing 1 factor at a time from its low to high values. The interaction terms (X_1X_2) show how the response changes when two factors are simultaneously changed. The polynomial terms (X_1^2 and X_2^2) are included to investigate nonlinearity. The dissolution profile for 9 batches showed a variation (i.e., initial 1 hr release ranging from 8.37% to 20.28% and drug released after 12 hr ranging from 73.91% to 101.31% as shown in Figure 1). The data indicate that the release profile of the drug is strongly dependent on the selected independent variables. The fitted equations relating the responses, Q_1, Q_8, $T_{50\%}$ to the transformed factor are shown in the Table 1. The polynomial equations can be used to draw conclusions after considering the magnitude of

coefficient and the mathematical sign it carries (i.e., negative or positive). Table 3 shows the results of analysis of variance (ANOVA), which was performed to identify insignificant factors. Data were analyzed using Microsoft Excel.

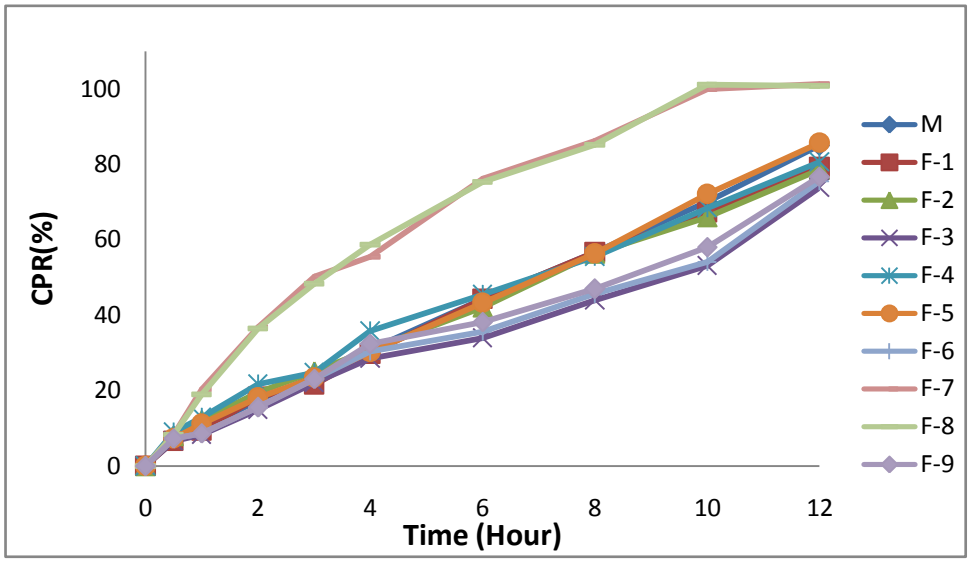

Figure 1 : Comparision of the Cumulative Percentage Drug Release of Factorial Batches

Table 3: Summary of Results of Regression Analysis

	Q_1		Q_8		$T_{50\%}$	
	Coefficients	**P-value**	**Coefficients**	**P-value**	**Coefficients**	**P-value**
Intercept	12.812	0.002	59.296	0.002	6.758	0.003
X_1	3.005	0.018	10.243	0.041	-0.965	0.106
X_2	-2.788	0.022	-10.327	0.040	-1.335	0.051
$X_1 X_2$	-2.655	0.042	-6.650	0.164	-1.515	0.061
X_1^2	2.032	0.161	10.057	0.144	-1.732	0.098
X_2^2	-2.788	0.084	-10.173	0.141	1.488	0.134
R square	0.9549		0.9217		0.9180	

R^2 value for Q_1, Q_8 and $T_{50\%}$ are 0.9549, 0.9217 and 0.9180 respectively indicating good correlation between dependent and independent variables. The terms with $P<0.05$ were considered statistically significance.

Kinetic modeling of dissolution data

The dissolution profile of all batches were fitted to various models such as zero order, first order, Higuchi, Hixon Crowell, Korsemeyer and Peppas (Table 4). In case of the controlled or sustained release formulations, diffusion, swelling and erosion are the three most important rate controlling mechanisms. Formulation containing swelling polymers show swelling as well as diffusion mechanism because the kinetic of swelling include relaxation of polymer chains and imbibitions of water, causing the polymer to swell and changing it from a glassy to rubbery state. The diffusion exponent n is the indicative of mechanism of drug release from the formulation. For a

swellable cylindrical (tablet) drug delivery system, When n<0.5, the drug diffuses through the polymeric matrix by a Fickian (case I) diffusion mechanism. For 0.5<n<1, an anomalous (non-Fickian) transport occurs i.e. the release is ruled by both diffusion of the drug and dissolution of the polymer. n=1 indicates case II transport and n> 1 indicates super case II transport release mechanism.[20],[21] The value of diffusion exponent n for all factorial formulations is more than 0.5 and less than 0.5 as shown in Table 4 indicating the drug diffuses through the polymeric matrix by an anomalous (non-Fickian) transport.

Table 4: Drug release kinetic study

Batch	Zero Order		First order		Higuchi		Hixson Crowell		Korsmeyer-peppas		
	K_0	R^2	K_1	R^2	K_H	R^2	K_{HC}	R^2	K_{KP}	n	R^2
M	3.831	0.999	1.021	0.909	19.88	0.964	0.971	0.971	9.626	0.983	0.983
F-1	4.081	0.997	0.995	0.885	18.82	0.974	0.990	0.990	9.798	0.991	0.991
F-2	6.375	0.999	1.069	0.896	15.35	0.974	0.987	0.987	9.876	0.995	0.995
F-3	3.950	0.980	0.963	0.892	14.97	0.941	0.941	0.941	9.613	0.983	0.983
F-4	7.831	0.995	1.110	0.888	14.24	0.977	0.984	0.984	9.821	0.992	0.992
F-5	3.752	0.999	1.027	0.911	20.02	0.959	0.966	0.966	9.781	0.990	0.990
F-6	4.671	0.978	0.991	0.888	14.67	0.944	0.940	0.940	9.535	0.979	0.979
F-7	18.196	0.933	1.288	0.712	13.48	0.990	0.929	0.929	9.268	0.967	0.967
F-8	8.029	0.931	0.076	0.715	35.217	0.990	0.494	0.888	9.342	0.970	0.771
F-9	5.686	0.985	0.082	0.883	23.833	0.956	0.130	0.956	9.559	0.980	0.757

M indicate the batch of marketed formulation (Uterest SR tablet, Serum international).

Comparison of dissolution profiles for selection of optimum batch

The values of similarity factor (f_2) for batches F_1 to F_9 were shown in Table 1. The batch F_5 showed maximum value of f_2 (93.02), hence was selected as optimum batch.

CONCLUSION

Formulation of sustained release tablets containing isoxsuprine HCl using HPMC K15M and PVP K25 was found to be potential, cost effective and satisfactory *in vitro* release studies. Tablets release the drug in a sustained manner for prolonged time depended on the percentage of polymers and thereby accompanying some of the benefits like reduction in total dose, frequency of administration, dose related side effects and better patient compliance.

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