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Formulation and Evaluation of Sustained Release Matrix Tablets of Isoxsuprine Hydrochloride by Direct Compression Method

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ABSTRACT

A sustained-release tablet formulation should ideally have a proper release profile insensitive to moderate changes in tablet hardness that is usually encountered in manufacturing. Isoxsuprine hydrochloride is structurally a novel vasodilator. The short biological half-life (5±2 hr) and the fast clearance make the drug, a suitable candidate for the development of modified release formulation. A novel oral controlled delivery system for isoxsuprine hydrochloride was developed and optimized. Matrix tablets of isoxsuprine hydrochloride were prepared by using hydroxypropylmethylcellulose (HPMC K15), Gaur Gum and PVP K 30 as polymer substance to achieve required sustained release profile. The matrix tablets were prepared by direct compression method which is now days considered a cost effective and simple method of manufacturing. It is considered as an appropriate method for hygroscopic and thermolabile substances. Six formulations of different polymer percentages were formulated (F1-F6). Pre-compression parameters were evaluated. The influence of matrix forming agents and binary mixtures of them on isoxsuprine hydrochloride release was investigated. The formulated tablets were characterized by hardness, friability, thickness, weight variation and *in vitro* drug release. The formulated tablets had acceptable physicochemical characters. There was no chemical interaction found between the drug and excipients throughout FT-IR and UV study thought of in the present investigation. The quantity of isoxsuprine hydrochloride present in the tablets and the release medium were estimated by a simple, rapid and validated UV method. The dissolution results show that increased amount of polymer resulted in reduced and extended drug release. F4 formulation is the optimum formulation due to its better targeting profile in terms of release. First order kinetic profiles were achieved. This formulation may provide an alternative for oral controlled delivery of isoxsuprine hydrochloride and be helpful in the future treatment of peripheral vascular disease.

Keywords: Isoxsuprine hydrochloride, HPMC K15, Gaur Gum, PVP K30, Direct compression method, Dissolution

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INTRODUCTION

Isoxsuprine hydrochloride is structurally a novel vasodilator[1]. The short biological half-life (5±2 hr) and the fast clearance make the drug, a suitable candidate for the development of modified release formulation. Oral administration of drugs is generally preferred, especially over parenteral administration. Oral products are produced in a more cost-effective manner in comparison with parenteral products and account for approximately 60% of all prescription products worldwide[2]. Sustained-release oral drug products are designed to slowly release the active ingredient over an extended time following administration and offer significant advantages over conventional orally administered products, including reduce side effects, increase safety and patient compliance by reducing the frequency of dosing and decreased drug plasma-concentration fluctuations[3,4]. Matrix formulations of hydrophilic and/or hydrophobic polymers have been used to control the release of drugs[5,6] and can be produced using conventional processing equipment. Formulation based on a hydrophilic matrix was chosen, since it is known to give robust formulae that can be manufactured by standard tabletting technology. In addition, it is possible to manufacture such formulations without using organic solvents; environmental risks associated with such solvents cause great concern and they often yield trace residues in finished products. To control and modulate drug release properties of tablets, retardant polymers including hydrophilic polymers such as HPMC and guar gum have been utilized in solid dosage forms. For these reterdants, hydrophilic polymers control drug release from tablets by hydrogelation[7,8]. HPMC has been employed extensively as

hydrophilic matrix former in oral controlled-release dosage forms for different drugs. Its popularity can be attributed to the polymer's non-toxic nature, small influence of processing variables on drug release, ease of compression and its capability to accommodate high levels of drug loading, its ability to swell upon jellification once in contact with water[9-11]. Thus, an attempt has been made to formulate the extended-release matrix tablets of Isoxsuprine hydrochloride and tested for controlled delivery of drug using matrix polymer.

MATERIALS AND METHODS

Materials

Isoxsuprine hydrochloride was procured from Corel Pharma Chem, Ahmedabad, India. HPMC K15, guar gum and PVP K30 was obtained from Central Drug House (CDR), Delhi. Lactose and Talc was purchased from Loba chem Pvt. Ltd., Mumbai (India) and magnesium stearate was purchased from Moly Chem. Mumbai (India). All other solvents and reagents were purchased from Merck (Germany) and were of analytical grade.

Methods

Preformulation studies

Solubility study

The drug sample was qualitatively tested for its solubility in various polar, semi polar and non polar solvents**.** Solubility of the drug was determined by taking about 10 mg of drug sample in a test tube containing 2.0 ml of solvent and shaking for 10 min at room temperature and observed for its solubility.

FT-IR spectroscopy

Infra- red spectrum is an important record which gives sufficient information about the structure of a compound. This technique provides a spectrum containing a large number of absorption band from which a wealth of information can be derived about the structure of an organic compound. The region from 0.8 μ to 2.5 μ is called Near Infra-red and that from 15 μ to 200 μ is called Far infra-red region. Approx 5 mg of drug was mixed with KBr and prepared their pallet. Pallet was analyse using FT-IR spectrophotometer (Bruker, USA).

Determination of λ_{max} of isoxsuprine hydrochloride

The λ_{max} of Isoxsuprine hydrochloride was determined by analyzing the drug solution in double beam ultraviolet spectrophotometer. Accurately weighed 10 mg of drug was dissolved in 10 ml of 0.1 N HCL solutions in 10 ml of volumetric flask. The resulted solution was 1000μg/ml of strength and from this solution 1 ml solution was pipette out and transfer into 10 ml capacity of volumetric flask and volume was made upto 10 ml with 0.1 N HCL solutions. This solution was scan at wavelength 400-200 nm on UV spectrophotometer (Labindia-3000 Plus). The higher absorption peak was obtained at 277 nm which was the λmax of drug.

Compatibility studies of drug and excipients

In the compatibility testing program, blends of drug and excipients are prepared by triturating the drug with Individual excipients. Mixture of Isoxsuprine hydrochloride (50 mg) and excipients (50 mg) was prepared and transferred to inert glass vials. Vials were covered with rubber closures followed by the aluminum seal caps. The vials were stored at 4˚C (refrigerator) as control and at 40˚C/75%RH for accelerated temperature condition for 4 weeks. The visual observations (color, flow, & sticking) were recorded. Sample were analyze for any interaction by using UV spectrophotometer (Labindia-3000 Plus).

Method for preparation of sustained release isoxsuprine hydrochloride matrix tablets

Sustain release matrix tablets were prepared by direct compression method. Accurately weighed quantity of all the excipients and drug such as Isoxsuprine hydrochloride, HPMC K15, gaur gum, PVP K30, magnesium stearate and talc were mixed and passed from 16 no sieve. Then blend was feed in hopper and tablets were prepared by direct compression using multi station automatic rotatory punching machine. The tablets were prepared using the punch of 8 mm diameter using the rotary tablet processing machine. The composition of formulation was given in table 1.

Table 1 Composition of SR matrix tablet of isoxsuprine hydrochloride

S. No.	Ingredients	F1	F2	F3	F4	F5	F6
1	Isoxsuprine hydrochloride	10	10	10	10	10	10
2	HPMC K15	70	80	90	-	-	-
3	Gaur Gum	-	-	-	70	80	90
4	PVP K 30	5	5	5	5	5	5
5	Lactose	150	140	130	150	140	130
6	Talc	10	10	10	10	10	10
7	Magnesium Stearate	5	5	5	5	5	5
Total Weight		250	250	250	250	250	250

Evaluation of isoxsuprine hydrochloride SR matrix tablets

Pre-compression Parameters

Angle of repose

The angle of repose of blends was determined by the funnel method. The accurately weighed blend was taken in the 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 blend. The blend was allowed to flow from the funnel on the surface. The diameter and height of the heap formed from the blend were measured. The angle of repose was calculated using the following formula[12].

$$\text{Tan } \theta = h/r$$

Where, "h" is the height of the heap and "r" is the radius of the heap of granules.

Bulk density (BD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced in to a measuring cylinder. The volume occupied by the powder was measured which gave bulk volume. The BD of powder blends was determined using the following formula[13].

$$\text{Bulk density} = \frac{\text{Total weight of powder}}{\text{Total volume of powder}}$$

Tapped bulk density (TBD)

An accurately weighed powder blend from each formula was lightly shaken to break any agglomerates formed and it was introduced into a measuring cylinder. The measuring cylinder was tapped until no further change in volume was noted which gave the tapped volume. The TBD of powder blends was determined using the following formula[14].

$$\text{TBD} = \frac{\text{Total weight of powder}}{\text{Total volume of tapped powder}}$$

Carr's compressibility index

The Carr's compressibility index was calculated from bulk density (BD) and tapped density of the blend. A quantity of 2 g of blend from each formulation, filled into a 10 ml of measuring cylinder. Initial bulk volume was measured, and cylinder was allowed to tap from the height of 2.5 cm. The tapped frequency was 25 ± 2/min to measure the tapped volume of the blend. The BD and tapped density were calculated by using the bulk volume and tapped volume.

Carr's compressibility index was calculated using the following formula[15,16].

$$\text{Carr's compressibility index (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's ratio

It is the measurement of frictional resistance of the drug. The ideal range should be 1.2-1.5, it was determined by the ratio of tapped density and bulk density.

HR = Tapped Density/ Bulk Density

Post-compression parameters

Shape of tablet

Directly compressed tablets were examined under the magnified lens for the shape of the tablet.

Thickness

Twenty tablets from the representative sample were randomly taken and individual tablet thickness was measured by using digital vernier caliper[17].

Hardness

Tablet hardness was measured by using Monsanto hardness tester. From each batch six tablets were measured for the hardness and average of six values was noted along with standard deviations.

Friability test

From each batch, ten tablets were accurately weighed and placed in the friability test apparatus (Roche friabilator). Apparatus was operated at 25 rpm for 4 minutes and tablets were observed while rotating. The tablets were then taken after 100 rotations, de dusted and reweighed. The friability was calculated as the percentage weight loss.

% friability was calculated as follows

$$\% \text{ Friability} = (W1 - W2) \times 100/W1$$

Where W1 = Initial weight of the 10 tablets, W2 = Final weight of the 10 tablets after testing.

Friability values below 0.5-1% are generally acceptable[18].

Weight variation test

To study weight variation individual weights (WI) of 20 tablets from each formulation were noted using electronic balance. Their average weight (WA) was calculated. Percent weight variation was calculated as follows. Average weights of the tablets along with standard deviation values were calculated.

Drug content

Tablets were weighed and then powdered by pestle in a mortar. 100 mg of powdered sample was taken in a beaker containing 20 ml of 0.1 N HCL to dissolve it. The content of the beaker was sonicated for 10 min to extract and dissolve out the drug from excipient particles. The solution was centrifuged at 3000rpm for 10 min and the supernatant was analyzed after suitable dilution at 277 nm using UV spectrophotometer (Labindia-3000 Plus). The mean percent drug content was calculated as an average of three determinations.

In-vitro drug release study

In-vitro dissolution studies of prepared tablets were carried out using USP Paddle type dissolution test apparatus. To determine the dissolution, 900 ml of 0.1N HCL was taken as dissolution media and filled in vessel and temperature was maintained at 37±0.5°C. Tablet was droped in vessel and rotates the paddle at speed of 50 RPM. The temperature of the medium was maintained at 37±0.5°C in whole the process. Sample (2 ml) was withdrawn at suitable time interval (30, 1, 2, 4, 6, 8, 10 and 12 hrs.) and filtered with pre weighted whatman filter paper. The samples were analyzed using UV spectrophotometer at λmax 277 nm. Equal amount of fresh dissolution medium was replaced after each withdrawal.

Kinetic analysis of dissolution data

To analyze the *in vitro* release data various kinetic models were used to describe the release kinetics. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent. Higuchi (1963) described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$C = K0\ t \qquad (1)$$

Where, K0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{LogC} = \text{LogC0} - K1\ t / 2.303 \qquad (2)$$

Where, C0 is the initial concentration of drug and K1 is first order constant.

$$Q = KHt1/2 \qquad (3)$$

Where, KH is the constant reflecting the design variables of the system.

$$Q01/3 - Qt1/3 = KHC\ t \qquad (4)$$

Where, Qt is the amount of drug remained in time t, Q0 is the initial amount of the drug in tablet and KHC is the rate constant for Hixson-Crowell rate equation.

The following plots were made using the in-vitro drug release data

Cumulative % drug release vs. time (Zero order kinetic model); Log cumulative of % drug remaining vs. time (First order kinetic model); Cumulative % drug release vs. square root of time

(Higuchi model) and cube root of initial concentration minus the cube root of percentage of drug remaining in the matrix vs. time (Hixson-Crowell cube root law) [18].

RESULTS AND DISCUSSION

Solubility of isoxsuprine hydrochloride was freely soluble in chloroform, ethanol and methanol, soluble in Phosphate Buffer pH 7.4 and in soluble in water. The melting point and pH of isoxsuprine hydrochloride was 202-203ºC and 4.12±0.01 respectively. Moisture content of isoxsuprine hydrochloride was found to be 0.06396 mg. λ_{max} of isoxsuprine hydrochloride was found to be 277 nm by using UV spectrophotometer (Labindia-3000 Plus) in linearity range 5-25 µg/ml Fig.1. Identification of isoxsuprine hydrochloride was done by FTIR spectroscopy with respect to marker compound. It was identified from the result of IR spectrum as per specification Fig.2. UV study was performed using spectrophotometer (Labindia-3000 Plus) instruments to determine the drug excipients compatibility study Fig 3 (A, B).

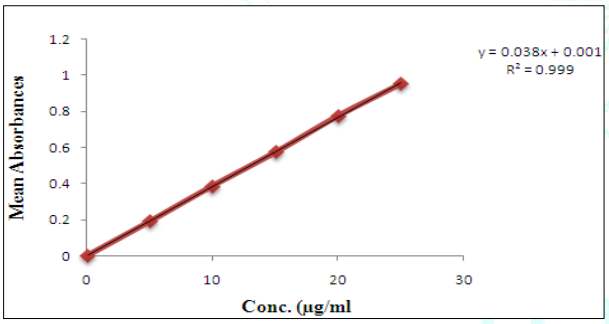


Fig.1 Calibration curve of isoxsuprine hydrochloride at 277 nm

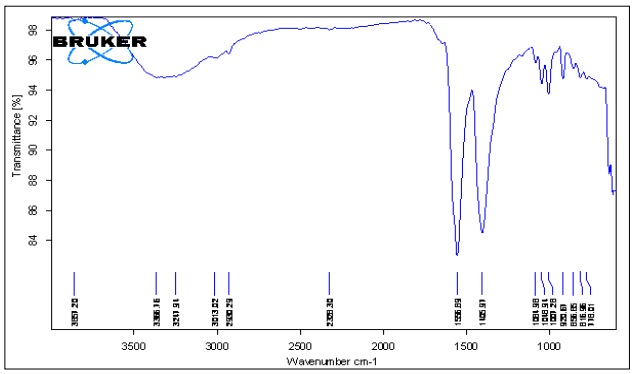
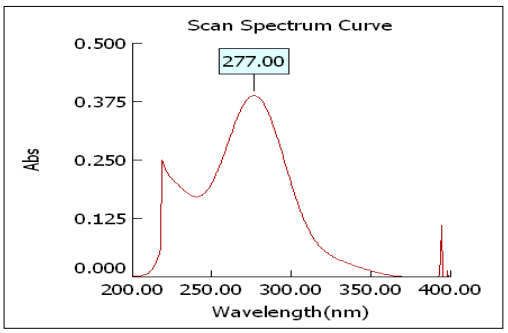
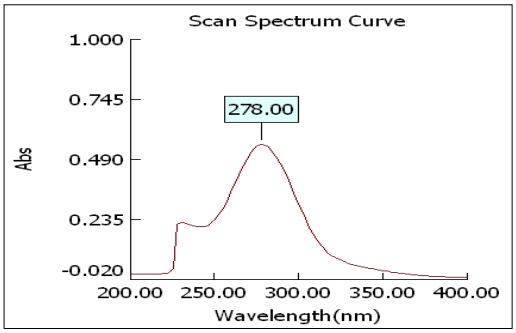


Fig. 2 FT-IR Spectrum of Pure Drug (isoxsuprine hydrochloride)



(A)



(B)

Fig. 3 UV spectra of isoxsuprine hydrochloride (A) isoxsuprine hydrochloride and Excipients (B)

Tablet powder blend was subjected to various pre-compression parameters Table 2. The angle of repose values indicates that the powder blend has good flow properties. The bulk density of all the formulations was found to be in the range of 0.34±0.02 to 0.37±0.06 (gm/ml) showing that the powder has good flow properties. The tapped density of all the formulations was found to be in the range of 0.46±0.03 to 0.48±0.10showing the powder has good flow properties. The compressibility index of all the formulations was found to be ranging between 21.74±0.21to 29.17±0.14 which show that the powder has good flow properties. All the formulations have shown the Hauser's ratio ranging between 0.10±0.06 to 0.14±0.05 indicating the powder has good flow properties.

The results of post-compression parameters such as the uniformity of weight, hardness, thickness, friability and disintegration time of the tablets are given in Table 3. All the tablets of different batches complied with the official requirements of uniformity of weight. The hardness of the tablets ranged from 3.9 to 4.3 kg/cm^2 and the friability values were less than 0.5% indicating that the matrix tablets were compact and hard. The thickness of the tablets ranged from 2.23 to 2.56 mm. All the formulations satisfied the content of the drug as they contained 95 to 98% of Isoxsuprine hydrochloride and good uniformity in drug content was observed. Thus all the physical attributes of the prepared tablets were found be practically within control.

Table 2: Result of Pre-compression characterization of powder blend for core tablet formulation

F. Code	Bulk Density	Tapped Density	Carr's Index	Hausner's Ratio	Angle of Repose
F1	0.35±0.05	0.47±0.08	25.53±0.12	0.12±0.08	30.25±0.22
F2	0.36±0.03	0.48±0.09	25.00±0.09	0.12±0.04	32.25±0.12
F3	0.34±0.02	0.48±0.10	29.17±0.14	0.14±0.05	30.12±0.32
F4	0.35±0.05	0.46±0.08	23.91±0.16	0.11±0.07	30.45±0.12
F5	0.36±0.04	0.46±0.03	21.74±0.21	0.10±0.06	32.25±0.32
F6	0.37±0.06	0.48±0.04	22.92±0.19	0.11±0.09	31.45±0.12

Table 3 Post-compression characterization of core tablet formulation

F. Code	Weight Variation (mg)	Thickness (mm)	Hardness (Kg/cm²)	Friability (%)	Drug Content (%)
F1	254±5	2.35	3.9	0.15	98.56
F2	251±8	2.32	4.1	0.16	95.56
F3	258±6	2.23	3.9	0.10	96.65
F4	256±8	2.36	4.2	0.17	98.98
F5	256±7	2.35	4.1	0.18	98.56
F6	249±5	2.56	4.3	0.19	98.23

All value are mean ± SD, n=3

The tablets were evaluated for in vitro dissolution studies in simulated gastric fluid pH 1.2. It was observed that tablets were remained intact in upper part of the GIT i.e simulated gastric fluid pH for 12 hrs. The results of the optimized formulation F3 showed maximum drug release i.e. 96.65±0.21 % at the end of 12 hrs. The results of release studies of formulations F1-F6 was shown in Table 4. The *in vitro* drug release data of the optimized formulation F3 was subjected to goodness of fit test by linear regression analysis according to zero order, first order kinetic equation, Higuchi's and Korsmeyer's models in order to determine the mechanism of drug release. When the regression coefficient values of were compared, it was observed that 'r' values of first order was maximum i.e. 0.988 hence indicating drug release from formulations was found to follow first order release kinetics Table 5.

Table 4 *In-vitro* drug release data for all formulation

Dissolution Media	Time (Hr)	Cumulative Drug Release (%)					
		F1	**F2**	**F3**	**F4**	**F5**	**F6**
Simulated Gastric Fluid (pH 1.2)	0.5	25.65±0.21	22.25±0.12	20.12±0.09	35.65±0.32	32.25±0.12	29.98±0.21
	1	35.65±0.25	33.32±0.45	30.12±0.21	40.15±0.21	35.65±0.25	34.65±0.12
	2	46.65±0.32	42.12±0.25	40.12±0.45	49.98±0.25	45.65±0.32	43.12±0.25
	4	68.98±0.45	65.65±0.32	62.48±0.23	60.45±0.26	59.98±0.14	55.45±.32
	6	88.98±0.32	85.45±0.14	83.12±0.25	75.36±0.21	74.65±0.12	71.12±0.14
	8	96.65±0.15	94.63±0.25	92.48±0.65	88.98±0.24	85.65±0.15	80.25±0.25
	10		97.98±0.12	94.65±0.14	96.65±0.15	98.78±0.19	96.65±0.26
	12			96.65±0.21			

Table 5 Regression analysis data

Batch	Zero Order	First Order
	R^2	R^2
F3	0.900	0.988

CONCLUSION

Direct compression methods can be used alternatively for wet granulation, because it is an easier, simplified and economical method of manufacturing of tablets. A number of research articles are available which are evident that the direct compression is a preferred method of tableting. Matrix tablet is one of the most convenient approaches for the preparation of the sustained release dosage forms. In actual practice direct compression of drug, retardant material, and additives is done to form a tablet in which drug particles are embedded in the matrix core of the retardant. It is concluded that modified release tablets of isoxsuprine HCl could be prepared using a HPMC K-15 and Gaur gum by direct compression method. The dissolution profile of the optimized formulation follows the first order release kinetics. The findings of this investigation can be extended to industry to cut down the cost of formulation. The sustained release matrix tablets of isoxsuprine HCl formulation system includes the drug delivery system that achieves slow and extended release of the drug over an extended period of time.

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