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Formulation and Evaluation Of Sustain Release Matrix Tablets of Levosulpiride

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ABSTRACT

The objective of the study was to develop oral sustained release matrix tablets of levosulpiride, in order to improve efficacy and better patient compliance. Tablets were prepared by wet granulation method using various hydrophilic polymers viz; HPMC K100LV and METHOCEL K4M are used. FT- IR study shown there no intraction between drug polymer and excipient .the physicochemical properties of tablets were found within limits. In-vitro drug release studies were performed using USP XXIII type II apparatus (paddle with hanging basket method). The drug release from formulation was extend for a preoid of 12. The Formulation (F5) shows the maximum drug release of 98.66% and also extended up to 12 hours.

Keywords: levosulpiride,metocel k100lv,k4m,wet granulation

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INTRODUCTION

The goal in designing sustained delivery systems is to reduce the frequency of the dosing or to increase effectiveness of the drug by localization at the site of action, reducing the dose required or providing uniform drug delivery. So, sustained release dosage form is a dosage form that release one or more drugs continuously in a predetermined pattern for a fixed period of time, either systemically or to a specified target organ. Sustained release dosage forms provide a better control of plasma drug levels, less dosage frequency, less side effect, increased efficacy and constant delivery. During the last two decades there has been remarkable increase in interest in sustained release drug delivery system. This has been due to various factor viz. the prohibitive cost of developing new drug entities, expiration of existing international patents, discovery of new polymeric materials suitable for prolonging the drug release, and the improvement in therapeutic efficiency and safety achieved by these delivery systems. Now-a-days the technology of sustained release is also being applied to veterinary products.

Schizophrenia

Based on our current knowledge of genetics and schizophrenia, no one gene causes the brain disorder on its own. Many of the common risk genes for schizophrenia are seen in healthy people, and they never develop the disorder. Researchers believe that this is because schizophrenia requires complex combinations of genes. But even with all the appropriate genetic risk factors, many (if not most) people may still not develop the disorder. This has lead to the examination of other influences besides genes, and their role in producing schizophrenia The Levosulpiride is an analytical antipsychotic agent, gastroprokinetic agent and schizophrenia also used that blocks the presynaptic dopaminergic D_2 recepters. Schizophrenia is a chronic disease so levosulpiride sustain release tablets required that have biological half life is 12 hours usual dosage regimen 200mg hpmc hydrophilic polymer are used like methocel k100lv and methocel k4m that non toxic and easy to handle.

The present study was deign to formulate sustain release matrix tablets of levosulpiride using k 100LVand k 4M polymer.

MATERIAL AND METHOD

Material

levosulpiride, Hypromellose(methocel k100lv,k4m, Povidone (pvp k30), isopropyl alcohol, Purified wate, microcrystailine cellulose, magnesium stearate, Colloidal silicon dioxide were procured commercially. All the reagents and solvents were used analytical grade.

Experimental Methods

Drug-excipient compatibility studies

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Compatibility studies is important part of the pre-formulation stage during the development of solid dosage form. Therefore, the pure drug and the formulations mixed with polymers and were subjected to FT-IR studies. The pure drug and formulations mixed with polymers were separately mixed with IR grade potassium bromide in a ratio (1:3000) and pellets were prepared by applying 10 metric ton of pressure in hydraulic press. The pellets were then scanned over range of 4000-400cm-1in FT-IR instrument. Then no intraction between the drug polymer and exipients.

Pre compressiom study of levosulpiride

(i) Angle of Repose

The angle of repose of granules, was determined by the fixed funnel and freestanding cone method, according to the method reported by Raghuram et al., * where by accurately weighed granules (5gm were carefully poured through the funnel with its tip at 2 cm height (h) until the apex of the conical heap so formed just reached the tip of the funnel. The mean diameter (r, of the base for the powder cone was measured and angle of repose (0) was calculated using the following equation.

$\tan\theta = h/r$

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

Where, θ = angle of repose

h = height

r = radius

Table--1

Angle of repose(Θ) (degrees)	Flow
<25	Excellent
25-30	Good
30-40	Passable
>40	Very poor

Bulk Density

Both loose bulk Density and tapped bulk density were determined, according to the method reported by raghuram et al, where by a quantity (20g) of granules from each formula, previously lightly shaken to break any agglomerates cylinder. After the initial volume was observed, the cylinder was allowed to full under its own weight onto a have surface from the height of 2.5cm at 2-Second intervals. The tapping was continued until no further change in the volume was noted loose bulk density (LBD) and tapped bulk density (TBD) were calculated using the following formulas

LBD = Weight of the powder/ volume of the packing

TBD = weight of the powder / tapped volume of the packing

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Hauser's Ratio

It indicates the flow properties of the powder and it measured by the ratio of TBD to the LBD

$$\text{Hauser's Ratio} = \frac{\text{TBD}}{\text{LBD}}$$

Table-2

S.NO	Hauser's Ratio	Property
1	0 - 1.2	Free flowing
2	1.2 – 1.6	Cohesive powder

Compressibility index (Carr's index)

To analyze flow ability, the Carr's index was calculated on the basis of the LBD and TBD. The compressibility index of the granules was determined by Carr's index

Carr's index (%) = [TBD – LBD) x 100)] / TBD

Table-3

% Carr's Index	Properties
5 – 12	Free Flowing
12 – 16	Good
18 – 21	Fair
23 – 35	Poor
33 – 38	Very Poor
>40	Extremely poor

Preparation of Levosulpiride Matrix Tablets

Six different tablet formulations were prepared by wet granulation technique as reported. The composition of 75mg levosulpiride of the drug:polymer ratio (HPMC K100LV METHOCEL K4M,) and filler micro crystalline cellulose (MCC) was dry mixed thoroughly 10 min. and binder preparation in non aqueous medium take pvp k30 dissolves in isopropyl alcohol.after wet mixing of the sufficient quantity of solvent is added after in the wet milling pass the wet mass in sieve #8 and then collect in clean container after wet granules are drying and pass sieve no #24 collect in polybag sufficient volume of granulating agent (5% wt/vol ethanolic solution of PVP-K 30). Sevieng of lubricant like magnesium and colloidal silicon dioxide that pass sieve no.#40 lubricate the granules for 10 minutes after the add magnesium stearate to the material mix for and the appropriate and then compressed using a 16 station tablet compression machine round, flat-faced punches of 6.05-mm diameter and die set and obtain % yield is 99.66 .All compressed tablets were stored in an airtight container at room temperature for the study.

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Table-4 Composition of 200mg Levosulpiride tablet

S.No	Ingredients (in mg)	F1	F2	F3	F4	F5	F6
1.	Levosulpiride	75	75	75	75	75	75
2.	METHOCEL K100 LV	37.5	75	112.5	--	--	--
3.	METHOCEL K4M	--	--	--	25	32	75
4.	Micro crystalline cellulose	80.9	48.2	5.7	92.7	85.7	42.7
5.	PVP K 30	4.4	4.4	4.4	4.4	4.4	4.4
6.	Iso propyl alcohol	q.s	q.s	q.s	q.s	q.s	q.s
7.	Magnesium Stearate	2.4	2.4	2.4	2.4	2.4	2.4
8.	Colloidal silicon dioxide	--	--	--	0.5	0.5	0.5

All ingredient in (mg)

Characterization of Tablets

The properties of the compressed matrix tablet, such as Hardness, Friability, weight variation & Drug content Uniformity, were studied.

Hardness Test

For each formulation, the hardness of 5 tablets was determined using a Monsanto hardness tester, mean and SD were calculated

Friability Test

For each formulation, 6 tablets were weighed. The tablets were placed in a friabilator (Roche friablator) and subjected to 25 rpm in 4 minutes. The tablets were then dedusted and reweighed. The friability was calculated as the percentages of weight loss.

$$F = 100 (1\text{-}wo/wt)$$

Where,

Wo = weight of tablets before friability test

Wt = weight of tablets after friability test

Weight variation Test

To study weight variation, to tablets of each formulation were weighed using an electronic balance and the test was performed according to the USP official limits of percentage deviation of tablet are presented in the table.

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Table-5 Weight variation Tolerance for uncoated Tablets

Average weight of Tablets (mg)	Maximum percentage Difference Allowed
80or less	10
80 – 240	7.5
More than 324	5

% maximum positive deviation = $(w_H\text{-}A/A) \times 100$

% minimum negative deviation = $(A\text{-}WL/A) \times 100$

Where

W_H = Highest weight in mg

WL = Lowest weight in mg

A = Average weight of tablet in mg.

Drug content uniformity

Standard preparation

An accurately weighed amount of pure levosulpiride (75mg) and transferred into 100ml volumetric flask. . It was dissolved and made up to volume with pH.7.4 phosphate buffer and absorbance was measured at 270 nm.

Sample preparation

Five tablets were weighed individually then placed in a mortar and powdered with a pestle. An amount of powdered levosulpiride (75mg) was extracted in buffer. The solution was filtered through 0.45µm membrane and absorbance was measured at 270 nm after suitable dilution.

Calculation

The amount of levosulpiride present in tablet can be calculated using the formula:

$$A_t/As \times S_w/100 \times 100/S_t \times A_v$$

Where,

A_t = Absorbance of sample preparation

A_s = Absorbance of Standard preparation

S_w = weight at lamivudine working standard (mg)

S_t = weight of lamivudine tablet (mg)

Av = Average weight of tablet (mg)

***In-Vitro* Drug Release Studies (Dissolution Studies)**

Dissolution Parameters

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Medium: 0.1N HCL, Phosphate buffer pH 6.8
Apparatus: USP-Type 2 (Paddlewith hanging basket)
RPM: 50
Temperature:$37^0 \pm 0.5^0$ C
Dissolution Medium: 900 ml

Procedure

The release of Levosulpiride from the SR tablet was studied upto 2 hrs in 900 ml of 0.1 N HCL and 900 ml of Phosphate buffer pH 6.8 upto 24 hrs as dissolution medium using a USP dissolution paddle assembly at 50 rpm and $37^o \pm 0.5^o$ C. An aliquot (5 ml) was withdrawn at specific time intervals, filtered and diluted to 10 ml with the dissolution medium, and drug content was determined by UV-visible spectrophotometer at 270 nm. An equal volume of fresh dissolution medium was replaced to maintain the dissolution volume. Dissolution studies were performed 6 times for a period of 12 hrs and the mean value were taken. Cumulative percentage of drug release was calculated using an equation obtained from a standard curve.

RESULT AND DISCUSSION

Preformulation Studies (Compatibility Studies)

Compatibility studies were performed by using FT-IR spectrophotometer. The IR Spectrum of pure levosulpiride drug was compared with the IR spectrum of physical mixture of levosulpiride (HPMC K100LV & K50 LV & EXIPIENTS).

There is no appearance or disappearance of any characteristics peaks. This shows that there is no chemical interaction between the drug excipient and the polymers.

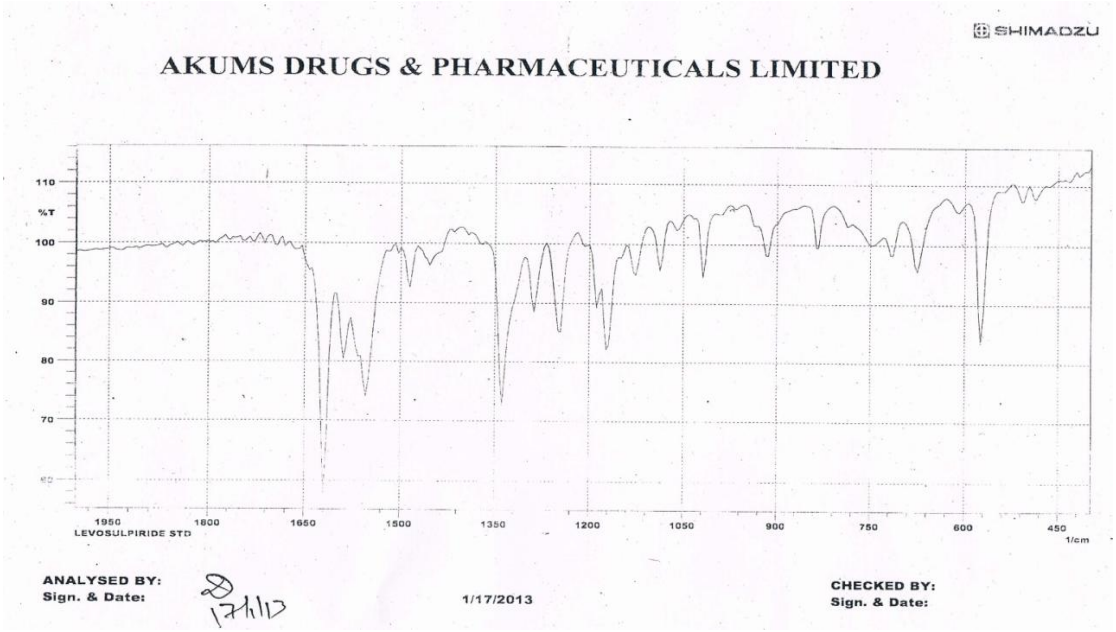

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Fig.1: Standard curve of Levosulpride

Table-6 Characteristic Absorption Peaks

Characteristic absorption Peaks at intensity	Functional gourps of levosulpiride	Observed peaks
1675-1600	(C=C) Alkenes	1620
1620-1535	(C.-.O)	1560
1370-1300	(N=O)	1325
1150-1070	(C-O)	1150

Table-7 Pre compression parameter

Formulation	Angle of repose	Bulk density	Tapped density	Carr's Index	Hausner's Ratio
F1	22.45	.456	.712	36.61	1.56
F2	22.56	.454	.723	36.20	1.59
F3	24.36	.461	.722	36.14	1.56
F4	24.78	.457	.719	36.40	1.57
F5	24.56	.456	.712	35.95	1.56
F6	23.89	.457	.718	36.35	1.57

Table-8 Post compression parameter of Levosulupiride

Formulation	Thickness (mm)	Hardness (Kg/cm2)	Friability (%w/w)	Weight variation (gm)	Content uniformity (%w/w)
F1	3.91	7.7	.20	200.34	98.78
F2	3.65	7.5	.12	201.04	99.32
F3	3.64	7.6	.24	200.89	98.99
F4	3.66	7.4	.11	199.45	99.45
F5	3.64	7.0	.13	200.19	99.98
F6	3.64	7.4	.20	201.68	98.13

Table-9 % drug release

Time (Hrs)	Formulations(mg)					
	F1	F2	F3	F4	F5	F6
1	43.76	28.48	30.08	26.21	30.68	32.65
2	73.71	41.31	44.41	33.25	46.28	47.89
4	85.44	62.80	67.62	52.64	70.89	68.03
6	101.73	75.90	82.13	78.23	86.95	87.64
8		89.67	95.52	87.43	92.52	90.59
12		107.58	94.59	96.25	98.66	96.26

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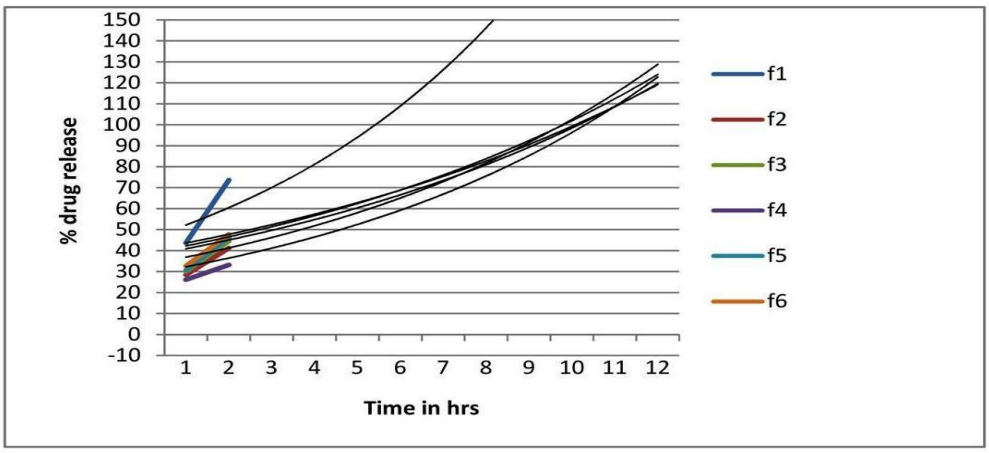

Fig 2

CONCLUSION

The study was undertaken with the aim to formulation and evaluation of levosulpiride sustain release matrix tablets using various concentration of polymers.sustain release levosulpiride tablets of 12 hrs which comparable with standard respectively HPMC k100lv and methocel k4m were found to be suitable as bases for preparing hydrophilic tablet matrix.

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