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FORMULATION AND EVALUATION OF SUSTAINED RELEASE TABLETS OF LEVOSULPIRIDE BY USING NATURAL

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ABSTRACT

Oral route has been the predominantly adopted due to its convenience for drug delivery. This route is considered significantly in the pharmaceutical field, due to its flexibility in formulating the dosage form than other routes. permeation through the other body tissue for effective pharmacological activity. For this justification, most system employed the sustained release. To study the impact of different polymers on drug release. To determine the kinetics and mechanism of drug release. To perform stability studies as per guidelines of ICH. To perform pharmacodynamics study To perform pharmacokinetic study.

This targeting concept is to achieve the patient compliance when compared to normal conventional dosage form. This is achieved by altering the pharmacokinetic parameters and improved pharmacodynamics. Levosulpiride was selected as a drug having soluble in intestinal pH. Levosulpiride plays a main role in treatment of Schizophrenia. The levosulpiride half-life is 4 to 6 hours. The plasma protein binding is less than 40%. Levosulpiride is rapidly absorbed with a bioavailability of over 25 to 30% following oral administration, hence it was considered as an ideal candidate for the design of oral sustained release dosage form.

In the present study, an effort was initiated to prepare the oral SR matrix tablets of levosulpiride to provide a dosage form for prolonged period of time, in order to improve pharmacologic efficacy, reduce the total dose frequency and improved patient compliance. Infrared spectroscopy and DSC analysis established the absence of any drug polymer interaction.

The resulting monolithic tablets were evaluated for official and unofficial tests like diameter, thickness, weight variation, hardness, friability and drug content. All the prepared tablet trials showed acceptable pharmaco technical properties passes the official pharmacopoeial standards. The *in vitro* release profiles were applied on various kinetic models. The release studies revealed that the release rate was decreased with increase in polymer proportion. From the results of present study it appears that the release of Levosulpiride was significantly influenced by the characteristics of polymer and excipients used. Invitro release from the formulation LF3 with the hardness of 7.96±0.06 kg/cm$^{2.}$ Higher hardness tablets contain a compact mass of polymer with relatively less pore, resulting in slower release. All other tested parameters of LF3 formulation were in the acceptable limits. So formulation LF3 was found to be better than other batch of formulation.

Keywords: Levosulpiride, Sustained Release Tablets, Formulations.

I. INTRODUCTION

ORAL DRUG DELIVERY SYSTEM

Oral route has been the predominantly adopted due to its convenience for drug delivery. This route is considered significantly in the pharmaceutical field, due to its flexibility in formulating the dosage form than other routes.1,2,3 This route of delivery depends on factors such system type, the disease, the diseased person and the duration of treatment and the characteristic property of the active medicament. Almost all the oral controlled drug delivery systems follow diffusion or dissolution mechanism of drug release in the GIT.4

The oral route can be utilized to target the required receptor region. This targeting concept is to achieve the patient compliance when compared to normal conventional dosage form. This is achieved by altering the pharmacokinetic parameters and improved pharmacodynamics. 5, 6, 7

Oral route has been used in ancient period also due to its convenience and among all route of delivery. For any medicine the oral route would be the primary choice due to its flexibility in drug delivery systems.

Oral route of administration has been used as either conventional or novel drug delivery system. Many advantages including patient willingness to accept and ease of administration. Sustained release system types given for oral route include virtually every at the present time now the theoretical mechanism. This is due to the manufacturing of dosage form is more flexible, since constraint, like sterility problem and harmful effects at

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site of administration are reduced. Perhaps, it is easy to develop different dosage forms by customary those developed for administration through oral route.

Regarding oral route, targeting is not of major consideration, and is u

Permeation through the other body tissue for effective pharmacological activity. For this justification, most system employed the sustained release.

Concentration of drug level it will increasing the rate absorption region and also, increase blood levels, in turn raise to higher concentration of active content at the targeted site of action.

SUSTAINED RELEASE DRUG DELIVERY SYSTEM

Over last 3 decades the expenditures and problems complicated in commercializing new molecules have increased, with identification of pharmacological merits of controlled/sustained delivery the initiation has begun to work on these novel drug delivery system. Many points to say about the attractiveness of these systems. It is generally considered in case of many diseases.

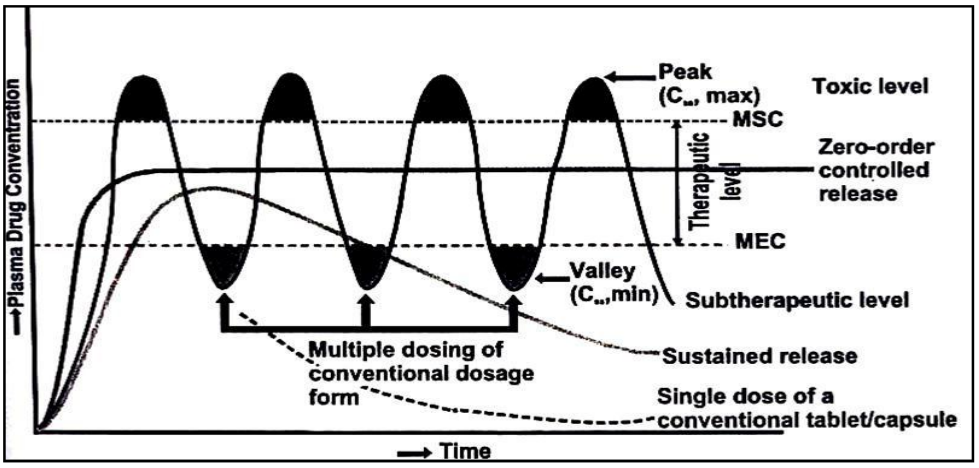

Figure 1.1: Plasma conc. VS Time (Conventional, Sustained and Controlled delivery)

AIM AND OBJECTIVES

Need of this work are:

The basic aim of any treatment is to accomplish a steady state level of active medicament in tissue/blood which is medicinally effective and safe for a specified time period. SRDDS with an objective of improved patient compliance, reduced side effects with reduced dose for treatment for acute and chronic diseases can be achieved.

Levosulpiride, a sulpiride isomer is a selective dopamine D_2 receptor antagonist that acts by blocking dopamine D_2 receptor. The levoform has more antidopaminergic, antiemetic and ant dyspeptic activity with reduced toxicity when compared to racemic and dextrose forms and showed unique pharmacokinetic properties. It is 40% bound with protein in circulation. Its plasma peak concentration occurs at 3 hours. It has a bioavailability of 25-30% with a distinct interindividual difference. It is slowly absorbed from the GIT. So, GI transient times have substantial effect on the controlled oral absorption of levosulpiride.

Matrix type tablets can be effectively used in the field of pharmacy for the sustained therapy.

Keeping all these points, the present research work has been aimed at formulating appropriate SR matrix tablets using polymers such as Xanthan gum, Guar gum and Chitosan.

Objectives

To execute reformulation studies such as flow properties & bulk density for powdered drug and other ingredients.

To formulate levosulpiride matrix tablets using wet granulation method. The polymers of natural type like Chitosan, Xanthan Gum and Guar gum were used.

To assess prepared formulations for basic physical limits like friability, weight variation, hardness etc.

To study *in-vitro* release performance of varioustablets formulations.

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To study the impact of different polymers on drug release.

To determine the kinetics and mechanism of drug release

To perform stability studies as per guidelines of ICH.

To perform pharmacodynamics study

To perform pharmacokinetic study.

PLAN OF WORK

The current research work was carried out to design SR tablets of Levosulpiride. It is an anti-psychotic drug. The SR tablets were prepared by classic wet granulation method using Chitosan, Xanthan gum, Guar gum, microcrystalline cellulose, PVP K30, isopropyl alcohol and magnesium stearate keeping in view the objectives described above the following plan of work was adopted.

THE SCHEME OF THE ENTIRE WORK IS LISTED AS FOLLOWS:

Review of literature

Selection of drug and additives

Purchase of drug and additives

Physicochemical studies (organoleptic properties, melting point and solubility)

Standardization of the method and construction of calibration curve for the estimation of Levosulpiride, quantification of drug

Compatibility studies by FTIR spectral and DSC studies

Formulation of levosulpiride SR matrix tablets by utilizing natural polymers like chitosan, xanthan and guar gum and by wet granulation technique

Evaluation of powder characteristics of granules

Angle of repose

Bulk density

Tapped density

Carr's index

II. LITERATURE REVIEW

Whiskey PJ, *et al.* (1999)[39] studied the roller compaction effect in the dry granulation. Niacin amide was prepared as controlled-release matrix tablets using HPMC, MC and magnesium stearate. The effects such as pressure of the roller, product recycles and drug release profiles were studied.

Reddy RK, *et al.* (2003)[40] formulated once daily SR matrix tablets of nicorandil. The drug is of choice for treatment of cardiovascular diseases due to its potassium channel opening property. The tablets were formulated by classic wet granulation using alcoholic solution of EC, Eudragit RL-100 and RS 100. HPMC, sodium carboxylic cellulose and sodium alginate. The granules were studied for physiochemical characteristics and for evaluation parameters. Granules showed good flow property and tablet formulations are all within official limits. From the dissolution studies the formulation F1 could extend the release for 24 hrs. and thus it exhibited the most successful formulation of the study.

Sandi BT, *et al.* (2003)[41] formulated tramadol hydrochloride matrix tablets using hydrophilic and hydrophobic polymers for controlled release. The influence of concentration of lyophobic and lipophilic polymers on active medicament release was studied. The tablets were organized by wet granulation and melt granulation method for lyophobic and hydrophobic matrix tablets respectively.

Saidan SM, *et al.* (2005)[42] developed diltiazem hydrochloride matrix tablets for controlled release using guar gum, microcrystalline cellulose, starch, magnesium stearate and talc. Dissolution studies were performed.

This activity of rats was measured using photoactometer (INCO, Ambala, India).

III. BIOCHEMICAL ESTIMATION

The animals were forfeited by cervical dislocation, entire whole brain was quickly frozen at -5 °C and brain dopamine levels was spectro fluorimetrically estimated by Ansell and Beeson10 method as revised by Cox and

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Perhach.

Statistical Analysis

The results were given in Mean ± S.E.M (n = 6). The statistical analysis of obtained data was performed by using ANOVA, followed by Dunnett's *t* test. If the probability is less than 0.05 was considered statistically significant.

PHARMACOKINETIC STUDY

The selected matrix tablet (LF3) was compared with marketed SR formulation (M1) of Levosulpiride to ascertain the bioequivalence of developed product. The experimental schedule has been approved by the institutional animal ethical committee (Registration number is XIX/VELS/PCOL /09/2000/ CPCSEA/ IAEC/03.10.2016)

The Wistar rats fasted overnight were separated into three sets each containing six animals.

Group I - levosulpiride pure suspended in 0.5 % CMC in distilled water

Group II - formulated granules of levosulpiride sustained release tablet suspended in

0.5% CMC in distilled water.

All the three groups the received oral dose of 5 mg levosulpiride/kg body weight.

The blood samples were collected from the orbital sinus of animals during 0.5, 1.0, 2.0, 4.0, 6.0, 8.0 and 12.0 h of time intervals into heparinized tubes. The collected blood was exposed to separation of plasma immediately by cold centrifuge at 3000 rpm for 15 min. The separated plasma was kept at -20 °C until analysis.

The concentration of levosulpiride in plasma was determined by HPLC method. Chromatographic condition- HPLC system contained of Shimadzu SPD10ATVP pump and rheodyne injector with 20 µL fixed volume loop and shimadzu SPD10A UV detector controlled by the software kinetica. Separation was carried out at room temperature phenomenax C18 (150.0 mm × 4.6 mm with 5 µ particle size) column. The mobile phase used in this experiment was methanol and 0.002 % formic acid, 5mmol/L ammonium acetate in water (80:20). The detector wavelength was set at 292 nm. Overall run time was 8 min. The injection volume was 5 µL. Retention time of levosulpiride and IS were 2.79 and 2.93 min.

IV. RESULTS AND DISCUSSION

PREFORMULATION STUDIES

Identification of Drug

FTIR spectroscopy

The levosulpiride FTIR spectrum was shown in Figure 1 and the interpretations of FTIR were showed in Table 7.1.

And the functional group connected with these peaks. The major peaks are identical to functional group of levosulpiride. Hence, the drug sample was confirmed as levosulpiride.

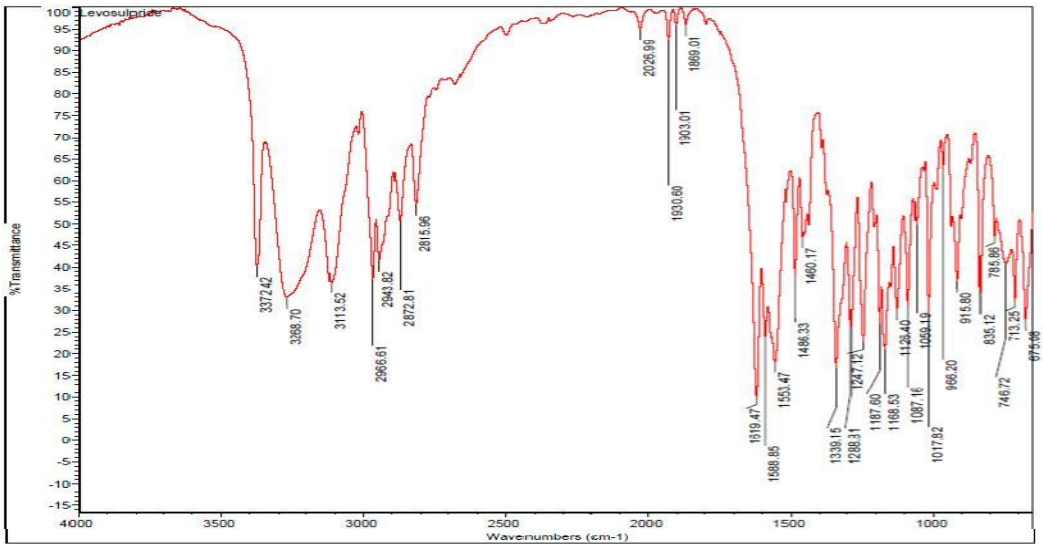

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Table 1 Characteristic bands in FTIR spectrum of Levosulpiride

Wave No.(cm^{-1})	Functional group
3372.42	O-H stretching
3268.70	C-H stretching
3113.52	Aromatic C-H stretching
2996.61	Methyl C-H stretching
1619.47	NH bending
1588.85	C=O stretching
1486.33	C-C ring stretching
1339.15	C-H bending
1017.82	S=O stretching
915.80	Out of plane C-H bending

Melting point

The physical parameter melting point of levosulpiride was found to be 185.66^{0}C. The reported melting point for levosulpiride was in range of 183 to 186^{0}C. The values of experiments are in follows with official values.

Physicochemical Parameters of Levosulpiride

Organoleptic properties

Odour : Odorless

Colour : A White (or) almost white crystalline powder

Taste : Bitter taste'

Solubility study

Table-2: Solubility studies of Levosulpiride

Experiment	Property	Observation
Solubility	Distilled water	0.052 - 0.007 mg / mL
	0.1 N HCl	0.097 - 0.018 mg / mL
	Phosphate buffer pH 6.8	7.086 - 0.052 mg / mL

All the above readings are average of three determinations ± SD

The solubility study of the drug was performed to choice a appropriate dissolution medium for *in vitro* drug release. The studies were done in triplicate. The solubility of levosulpiride in distilled water was very low 0.052 - 0.007 mg / mL. At pH 1.2, the solubility in 0.1 N hydrochloric acid was 0.097 ⍰ 0.018 mg / mL. At a pH of 6.8, the solubility in phosphate buffer was 7.086 ⍰ 0.052 mg / mL. Since the solubility of the drug is pH dependent, it is more significant to use both acidic and alkaline media for *in vitro* studies of sustained release tablets to simulate gastrointestinal tract.

Analytical Methods

Estimation of absorption maximum in 0.1 N HCl

The levosulpiride absorption maximum was identified to be 290 nm.

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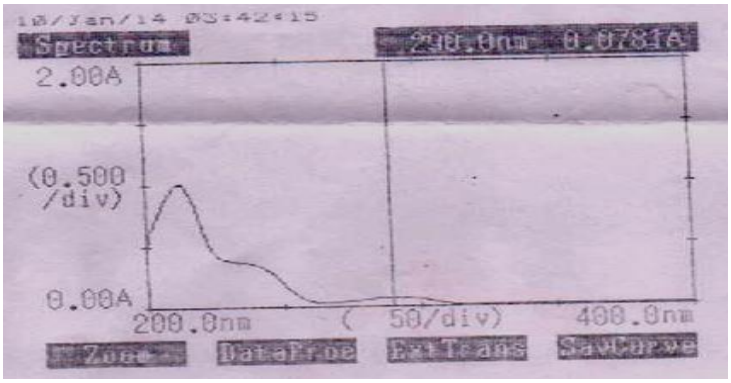

Figure 2 Z_{max} for Levosulpiride in 0.1N HCl

Determination of absorption maximum in pH 7.4 phosphate buffer

The levosulpiride absorption maximum was identified to be 290.5 nm.

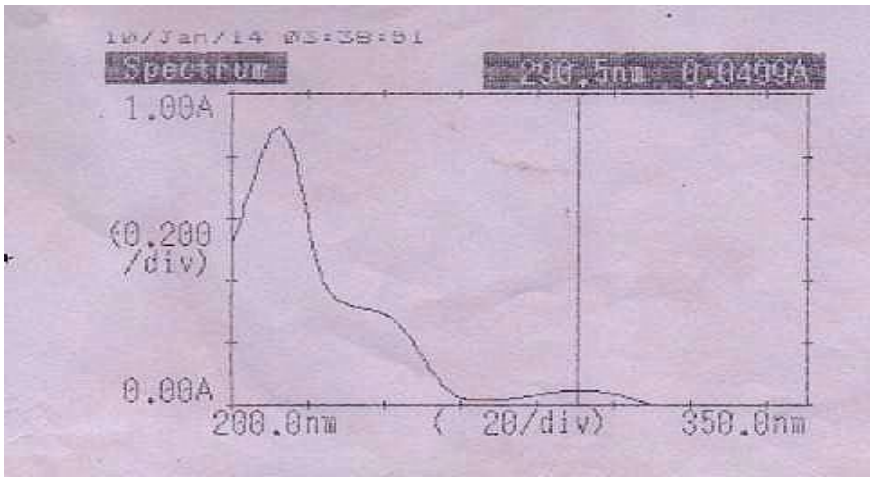

Figure-3: Z_{max} for levosulpiride in pH 7.4 phosphate buffer

Preparation of standard curve of levosulpiride in 0.1 N HCl

The levosulpiride UV absorption spectrum in 0.1N HCl showed Z_{max} at 290 nm. The absorbance obtained for different concentrations of levosulpiride in 0.1N HCl were given in Table 3. The curve absorbance VS concentration for levosulpiride was found to be linear in the concentration range of 0–50 µg/ ml. Hence it obeys Beer- Lambert's law in the concentration range of 0–50 µg/ ml.

Table -3: Concentration and absorbance of Levosulpiride in 0.1N HCl

S. No.	Concentration (µg/ml)	Absorbance
1	0	0.000
2	10	0.086
3	20	0.179
4	30	0.270
5	40	0.359
6	50	0.448

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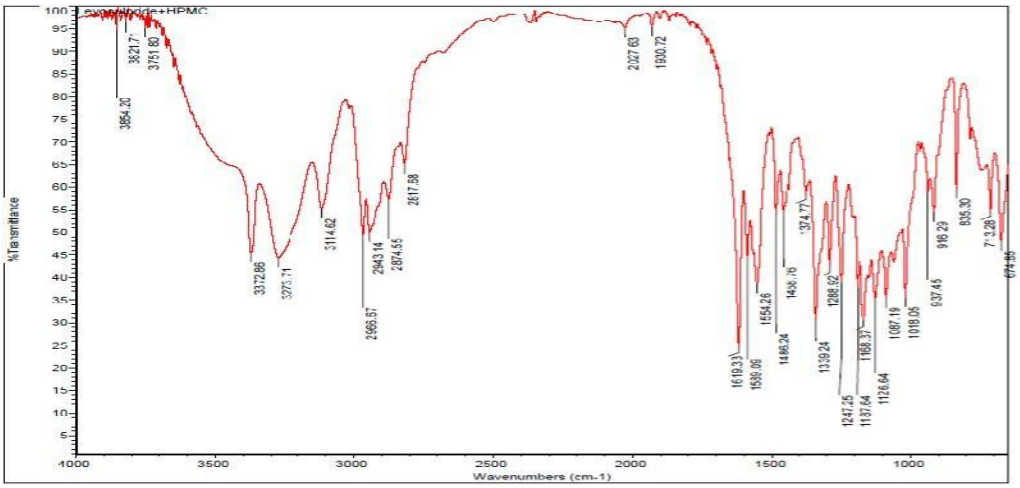

Figure-4: FTIR spectrum of Levosulpiride with Chitosan

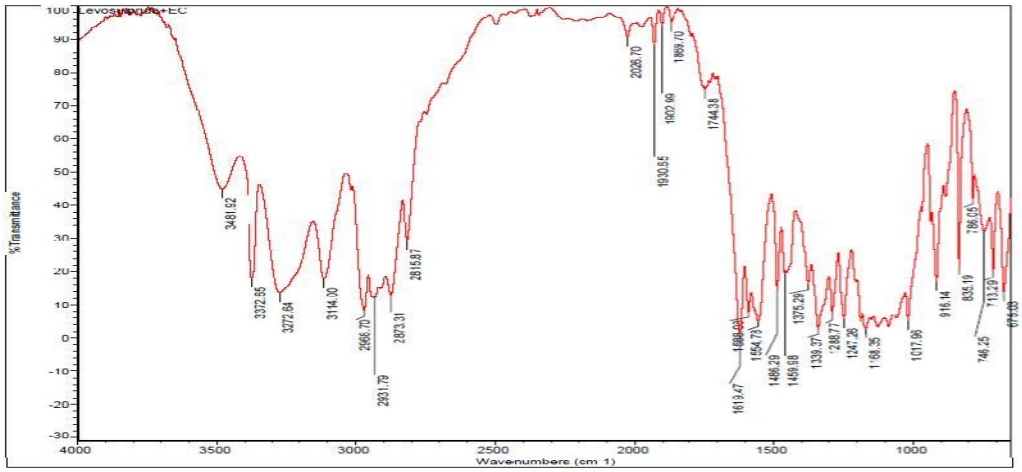

Figure-5: FTIR spectrum of Levosulpiride with Xanthan Gu.

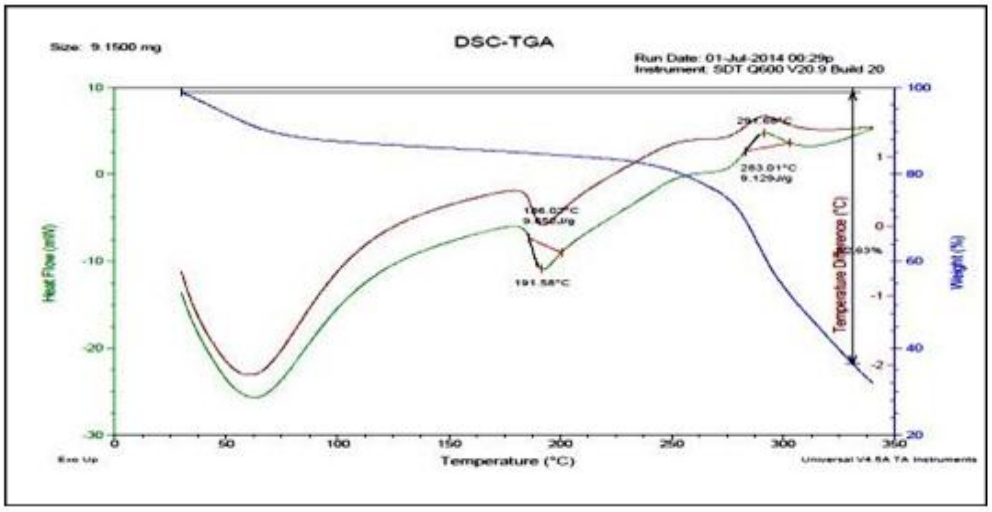

Figure-6: DSC thermal analysis of Levosulpiride + Guar Gum

According to Figures 7 to 10 and Table 4, DSC thermogram exhibited that there was no significant changes in onset, end and peak temperature when compared with pure drug thermogram. Therefore the results suggest that there was no interaction between levosulpiride and different polymers.

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Table-4: DSC thermogram parameters of Levosulpiride with various polymers.

S. No.	DSC thermogram	Onset temperature (°C)	Peak temperature (°C)	End set temperature (°C)
1	Levosulpiride	188.23	190.86	194.62
2	Levosulpiride + Chitosan	188.10	190.45	193.81
3	Levosulpiride + Xanthan Gum	188.01	190.17	193.09
4	Levosulpiride + Guar Gum	188.96	191.58	195.20

Compressibility Index (Carr's index)

The carr's index (%) ranged from 13.10±0.41 to 14.23±0.86 (Table No.5). The granules were found to have excellent flow property because the value was found to be below 15%.

Hausner Ratio

The Hausner ratio ranged from 1.15±0.01 to 1.17±0.01 (Table No.5).

The result designates the free flowing property

EVALUATION OF SR MATRIX TABLETS

Table 6: Physico-chemical parameters of Levosulpiride matrix tablets

F. Code	Dimension		Hardness (kg/cm²)	Friability (%)	Weight variation (mg)	Drug content (%w/w)
	Diameter (mm)	Thickness (mm)				
LF1	7.70±0.05	3.87±0.06	7.37±0.02	0.278±0.00	197.99±1.57	98.47±0.15
LF2	7.80±0.04	3.83±0.04	7.38±0.04	0.288±0.00	198.53±1.03	98.52±0.36
LF3	7.78±0.06	3.87±0.04	7.96±0.06	0.288±0.00	199.18±1.61	99.45±0.30
LF4	7.88±0.03	3.78±0.03	7.75±0.03	0.288±0.00	198.64±1.30	99.64±0.53
LF5	7.97±0.03	3.72±0.04	7.26±0.06	0.288±0.00	198.87±1.14	100.13±0.24
LF6	7.81±0.04	3.78±0.03	7.87±0.04	0.283±0.00	198.59±1.12	99.48±0.35
LF7	7.58±0.05	3.71±0.03	7.91±0.03	0.284±0.00	199.12±1.61	100.10±0.21
LF8	7.42±0.05	3.71±0.04	7.95±0.03	0.286±0.00	199.20±1.41	100.17±0.67
LF9	7.57±0.05	3.72±0.04	7.48±0.05	0.273±0.00	198.74±1.02	98.47±0.39
M1	7.72±0.03	3.76±0.04	7.94±0.04	0.280±0.00	198.94±1.61	100.08±0.58

All the values were expressed as mean ± SD, n=3

Tablet formulations prepared from the above ten formulations were evaluated for weight variation, hardness, thickness, friability and drug content.

Table-7: Dissolution of formulation LF4, LF5, LF6 & M1

Time (hours)	Percentage drug released*			
	LF4	LF5	LF6	M1
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	8.78±1.51	8.28±0.99	4.76±0.84	5.20±0.45
2	18.521±0.95	20.21±2.24	10.54±0.84	10.47±1.04
3	27.41±1.51	31.31±1.56	19.40±1.40	18.60±0.66
4	36.79±1.52	44.24±2.26	31.82±0.84	28.82±0.24

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5	47.11±1.73	55.04±2.27	46.07±1.41	35.54±1.50
6	56.17±0.98	61.06±1.59	55.24±1.40	48.28±1.08
7	63.95±1.54	71.07±1.23	63.22±0.86	62.06±0.90
8	72.22±1.55	79.38±1.23	70.73±1.41	70.82±1.42
9	96.41±1.54	85.09±1.04	84.79±0.81	78.16±1.06
10	96.70±1.00	95.08±3.15	90.91±0.82	85.94±0.82
11	96.94±1.51	95.39±1.03	94.83±1.42	88.15±0.50
12	96.99±2.26	95.74±0.29	94.95±0.87	95.02±0.74

*All values were expressed as mean ±SD, n=3.

Table-7: Dissolution of formulation LF7, LF8, LF9 & M1

Time (hours)	Percentage drug released*			
	LF7	LF8	LF9	M1
0	0.00±0.00	0.00±0.00	0.00±0.00	0.00±0.00
1	5.55±0.83	5.78±0.83	4.59±0.88	5.20±0.45
2	11.30±1.39	14.17±1.39	9.45±1.45	10.47±1.04
3	21.92±1.39	19.52±1.39	15.66±2.15	18.60±0.66
4	30.84±0.83	26.67±2.08	20.13±1.46	28.82±0.24
5	50.81±0.84	36.05±0.83	29.04±2.17	35.54±1.50
6	64.24±1.40	45.49±0.83	34.91±2.79	48.28±1.08
7	81.22±0.86	64.53±1.39	45.22±2.19	62.06±0.90
8	94.73±1.41	81.07±1.40	68.70±2.20	70.82±1.42
9	94.79±0.81	95.07±1.48	79.46±2.77	78.16±1.06
10	94.91±0.82	95.44±0.92	93.40±2.78	85.94±0.82
11	95.09±1.42	95.60±1.39	93.75±2.17	88.15±0.50
12	95.24±0.87	95.24±1.41	93.94±1.49	95.02±0.74

*All values were expressed as mean ±SD, n=3.

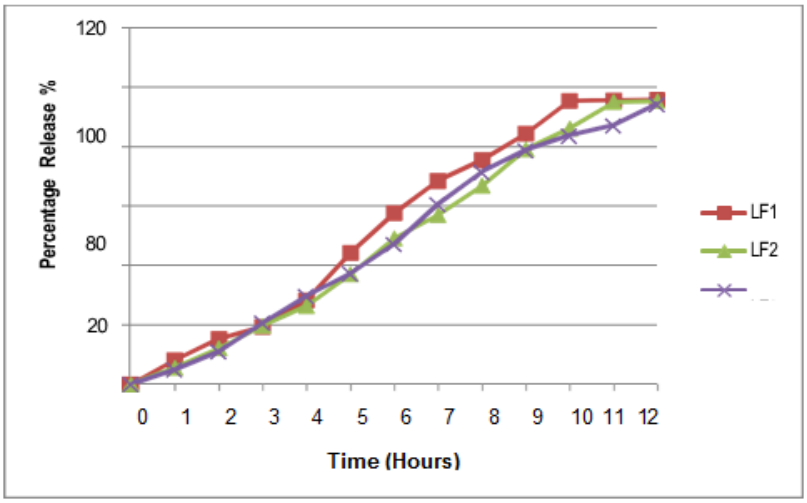

Figure 7: *In vitro* drug release profile of formulations containing Chitosan

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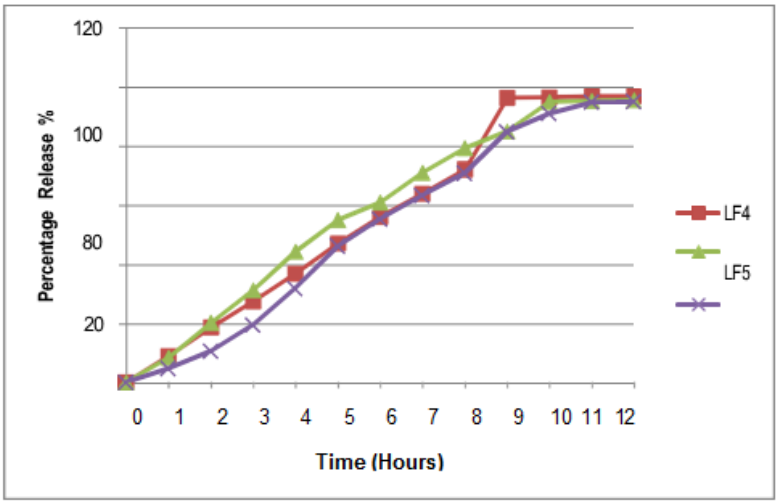

Figure :8: *In vitro* drug release profile of formulations containing Xanthan Gum

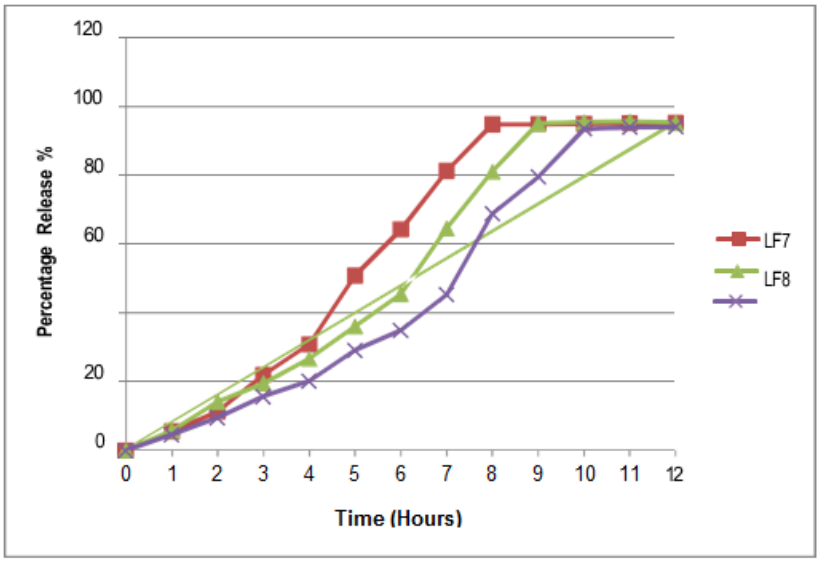

Figure -9: *In vitro* drug release profile of formulations containing Guar Gum

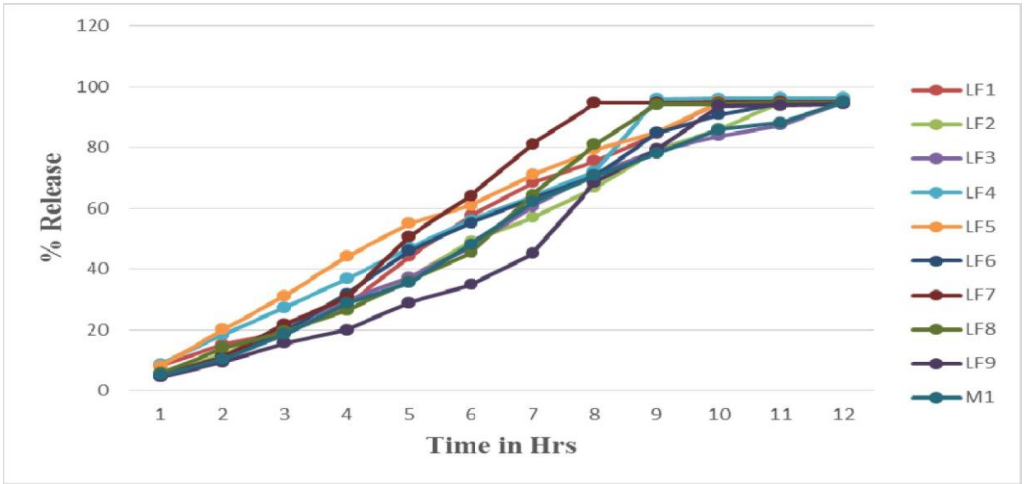

Figure-10 *In vitro* drug release profile of LF1 to LF9 and M1

The drug released from trials LF7 to LF9 containing Guar Gum at 3concentration levels of 25%, 50%, 75% were

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found to be 94.73 ± 1.41, 95.07 ± 1.48% and 93.40 ± 2.78 for Levosulpiride at the end of 8th,9th and 10th hours respectively. It was shown in Table 7.

The rate of drug release from Chitosan was found to be less when compared to Xanthan Gum and Guar Gum. This is due to slow hydration of matrix and to form a thick gel layer, which causes slow erosion and this character retard the drug release from the tablet for long duration.

The overall release rate of Levosulpiride from Xanthan and Guar Gum are significantly higher than that from Chitosan were shown in Figure 8. These results indicates that Chitosan has higher drug retarding capacity for long period than Xanthan and Guar Gum .

In addition to polymer concentration, the nature, type and viscosity also influences the release of drug. When drug release data obtained from dissolution study of different polymers at 25%, 50% and 75% concentration is plotted against time respectively, it was

tablets.

Table 8: Time of *in vitro* drug release for Levosulpiride $t_{50\%}$ values of LF1 to LF9 and M1.

Formulation code	Time of drug release (hours) ($t_{50\%}$)
LF1	5.25
LF2	6.1
LF3	6.15
LF4	5.20
LF5	4.50
LF6	5.30
LF7	5.00
LF8	6.15
LF9	7.10
M1	6.10

The LF3 formulation showed identical results with that of marketed formulation M1.

V. CONCLUSION

Oral route has been the predominantly adopted due to its convenience for drug delivery. This route is considered significantly in the pharmaceutical field, due to its flexibility in formulating the dosage form than other routes. This route of delivery depends on factors such delivery system type, the disease, the patient and the duration of therapy and the characteristic property of the drug. Almost all the oral controlled drug delivery systems follows diffusion or dissolution mechanism of drug release in the GIT.

Levosulpiride was selected as a drug having soluble in intestinal pH. Levosulpiride plays a main role in treatment of Schizophrenia. The levosulpiride half-life is 4 to 6 hours. The plasma protein binding is less than 40%. Levosulpiride is rapidly absorbed with a bioavailability of over 25 to 30% .

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