Design, Formulation and *In Vitro* Evaluation of Sustained-release Tablet Formulations of Levosulpiride

Levosulpirid Sürekli Salım Tablet Formülasyonlarının Tasarımı, Formülasyonu ve *İn Vitro* Değerlendirilmesi

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ABSTRACT

Objectives: Levosulpiride is a widely used gastroprokinetic agent in the treatment of various gastric disorders; however, its short half-life and increased dosage frequency leads to non-compliance and possible adverse effects. The prime objective of the current study was to develop a sustained-release formulation of Levosulpiride incorporating bioresorbable cellulose derivatives.

Materials and Methods: Sustained-release formulations of Levosulpiride were prepared through direct compression using various cellulose derivatives such as CMC sodium, HPC, and HPMC in different polymer-to-drug weight ratios as release-modifying polymers. The powder blends and compressed tablets were then subjected to pre-compressional and post-compressional evaluation, as well as FTIR analysis. *In vitro* release studies were performed for all formulations of the model drug in buffer solution of pH 6.8 at a wave length of 214 nm by a UV-visible light spectrophotometer.

Results: The FTIR results confirmed that the interaction between components was physical, and from the different kinetic models data, the release profile was best expressed by the Higuchi model because the results showed high linearity. The results also showed formulation F9 to be the ideal one among the developed formulations, exhibiting sustained- release behavior.

Conclusion: Levosulpiride sustained-release matrices were prepared successfully using CMC sodium, HPC, and HPMC as the release-retarding polymer/carrier.

Key words: Levosulpiride, sustained release tablets, dissolution, compliance, polymers

ÖZ

Amaç: Levosulpirid, çeşitli gastrik bozuklukların tedavisinde yaygın olarak kullanılan bir gastroprokinetik ajandır; bununla birlikte, kısa yarı ömrü ve artan dozlama sıklığı, uyumsuzluk ve olası yan etkilere yol açar. Bu çalışmanın asıl amacı, biyolojik olarak resorbe olabilen selüloz türevlerini içeren Levosulpiridin sürekli salımlı bir formülasyonunu geliştirmektir.

Gereç ve Yöntemler: Levosulpiridinin sürekli salım formülasyonları, salım modifiye eden polimerler olarak CMC sodyum, HPC ve HPMC gibi çeşitli selüloz türevlerinin farklı polimer-etkin madde ağırlık oranlarında kullanımıyla direkt basım yoluyla hazırlandı. Daha sonra, toz karışımları ve basılmış tabletler basım öncesi ve basım sonrası değerlendirmeye ve aynı zamanda FTIR analizlerine tabi tutuldu. UV/görünür ışık spektrofotometresi ile 214 nm dalga boyunda pH 6.8 tampon çözeltisinde model etkin maddenin tüm formülasyonları için *in vitro* salım çalışmaları gerçekleştirildi.

Bulgular: FTIR sonuçları, bileşenler arasındaki etkileşimin fiziksel olduğunu ve farklı kinetik model verilerinden, salım profilinin Higuchi modeline en iyi şekilde uyum gösterdiğini doğruladı, çünkü sonuçlar yüksek doğrusallık gösterdi. Sonuçlar ayrıca, geliştirilmiş sürekli salım formülasyonları arasında F9 formülasyonunun ideal olduğunu gösterdi.

Sonuç: Salım geciktirici polimer/taşıyıcı olarak CMC sodyum, HPC ve HPMC kullanılarak levosulpirid sürekli salımlı matrisler, başarıyla hazırlandı.

Anahtar kelimeler: Levosulpirid, sürekli salım tabletleri, çözünme, uyum, polimerler

INTRODUCTION

The oral route of drug administration is the most acceptable and frequently used route because of the convenience of self-administration, ease of manufacturing, and high-degree of dose accuracy.[1] Dosage forms are designed by exploiting the unique features of the gastro-intestinal tract (GIT) as the drug has to pass from the walls of GIT before getting access to the systemic circulation.[2] The pharmaceutical industry is focusing on the establishment of novel drug delivery systems rather than investigating and developing new drug entities due to the increased investigational cost of new drugs.[3] Over the past several decades, controlled-release technology has rapidly emerged as a drug delivery system that offers novel approaches for the delivery of bioactive compounds into systemic circulation at a predetermined rate, which significantly improves drug bioavailability and clinical outcomes with decreased toxicity. Sustained-release (SR) dose forms are designed in such a way that the rate of drug release from the tablet matrix occurs in a controlled manner over an extended period of time maintaining a constant plasma drug level thus improving patient compliance and effective clinical outcomes.[4] A constant therapeutic drug level is maintained throughout the dosing intervals, which often prolongs the onset of pharmacologic action.[5]

The development of sustained drug delivery systems is a challenging task in terms of providing a constant drug release profile retaining the dosage form in the stomach or upper small intestine until all the drug is completely released in the desired time.[6] An ideal oral drug delivery system will steadily release a measurable and reproducible amount of drug over an extended period of time.[7] Several mechanisms are involved in the release of drugs from controlled-release formulations such as dissolution- controlled release systems and diffusion-controlled release systems. In dissolution- controlled systems, dissolution is the rate-controlling step. The drug is embedded in slowly dissolving or erodible matrix or by coating it with slowly dissolving substances, whereas in diffusion-controlled release systems, the release rate of drug is dependent on its diffusion through an inert water insoluble membrane barrier. In matrix-diffusion controlled devices, the therapeutic agent is dispersed in an insoluble matrix of rigid non-swellable hydrophobic materials or a swellable (soluble) hydrophilic substance. Among different strategies to prolong the drug action, matrix tablet formulations have gained immense popularity because they have the advantage of simple processing and low-cost fabrication.[8] Matrix tablets are cost effective, easy to prepare, and exhibit predictable release behavior.

Polymers are becoming increasingly important in the field of drug delivery. They owe their unique properties to their size, three-dimensional shape, and asymmetry. Polymers occur naturally (biopolymers) as well as synthesized in the laboratory on a large scale. Advances in polymer science have led to the development of several novel drug delivery systems.[9] The chemical reactivity of polymers depends to a large extent on the way the monomer units are put together. Polymers can be used in film coatings to mask the unpleasant taste of a drug, to enhance drug stability, and to modify drug-release characteristics. Discovery of polymers with ideal properties still provides new avenues in pharmaceutical research.

Studies have shown that the rate and extent of drug release depends on the type and level of the excipient/polymer used. Many polymers have been used in the formulation of matrix-based SR drug delivery systems. Water-soluble polymers are being widely used in the designing of matrix systems in order to provide sustained drug delivery because of their excellent drug-retarding ability, low cost, and broad regulatory acceptance.[10,11] Hydrophilic polymers are usually not affected by variations in pH; therefore, they release the drug at a constant rate from oral dose forms. However, in the case of water-soluble drugs, the use of hydrophilic polymers alone for prolonging drug release is restricted because of the leakage of dissolved drug from the hydrophilic gel network through diffusion, hence a blend of hydrophilic and hydrophobic polymers is recommended for such drugs.[12] Among the cellulose ether derivatives, hydroxypropyl methyl cellulose (HPMC) has been widely investigated for its drug-releasing effect as compared with methyl cellulose and hydroxypropyl cellulose (HPC).[13]

Carboxy methyl cellulose (CMC) sodium, is described by the United States Pharmacopeia (USP) as the sodium salt of poly carboxy methyl ether of cellulose. CMC or cellulose gum, often used as a sodium salt, is a derivative of cellulose (a beta-glucopyranose polymer) with carboxy methyl groups ($-CH_2-COOH$) attached to the hydroxyl groups of the glucopyranose backbone. It occurs as white, odorless, granular powder with the molecular formula $[C_6 H_7 O_2 (OH)_2 CH_2 COONa]$ n. Figure 1 indicates the chemical structure of CMC sodium. A number of grades of CMC sodium are available such as Accelerate. Grades are typically classified as being of low, medium or high viscosity.

HPMC, also known as hypromellose, is propylene glycol ether of methyl cellulose. It is a semi synthetic, inert, visco-elastic polymer used as an ophthalmic lubricant, as well as an excipient and controlled-delivery component in oral medicaments. HPMC is the most important hydrophilic carrier material used in the preparation of oral controlled drug delivery systems because of its non-toxic nature, ease of compression and accommodation to high level of drug loading.[14] Figure 2 represents the chemical structure of HPMC.

HPC is a derivative of cellulose, soluble in both water and organic solvents. It has the property to retain water by forming a film that prevents water loss and exhibits greater drug retarding properties than hydroxyethyl cellulose. The drug release from HPC matrices is controlled primarily by diffusion through pores and channels in the structure.[15] HPC is generally used as an
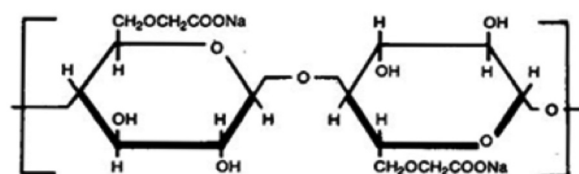

Figure 1. The chemical structure of carboxy methyl cellulose sodium

emulsifier, thickening agent, and film-former in tablet coatings because of its surface properties, but it lacks the property to form gel because it forms open helical coils. Figure 3 indicates the chemical structure of HPC.

Medicinal products of the prokinetics class are found to be effective in the treatment of all clinical forms of dyspepsia.[16] Levosulpiride, as a gastroprokinetic agent, has shown promising results in the treatment of various gastric disorders such as functional dyspepsia and non-erosive reflux disorder.[17] Chemically, it is a synthetic benzamide derivative with a strong inhibitory effect on dopaminergic D_2 receptors both in the central nervous system and in the GIT.[18] Studies have shown Levosulpiride to be effective in the treatment of various diseases such as dyspepsia (functional or organic), diabetic gastroparesis, reflux esophagitis, iatrogenic emesis induced by drugs such as chemotherapy, calcitonin, and anesthetics, as well as non-iatrogenic nausea and vomiting.[19] It also acts as a moderate agonist at the serotonergic 5-HT$_4$ receptor and to a lesser extent on 5-HT$_3$ receptors.[20,21] The serotonergic (5-HT$_4$) component of Levosulpiride may enhance its therapeutic efficacy in gastrointestinal disorders.[22] This property, together with antagonism at D2 receptors, may contribute to its gastrointestinal prokinetic effect.[17] In a randomized, double-blind trial, it was found that Levosulpiride had a similar effect to cisapride in the treatment of dysmotility-like functional dyspepsia.[23] The drug is given mostly at the dosage of 25-50 mg three times a day because of its short half-life, which leads to poor treatment adherence by patients and adverse drug effects. Figure 4 represents the structure of Levosulpiride.

The aim of the current work was an attempt to develop SR matrix tablets of Levosulpiride for improved patient compliance and better therapeutic effects of various polymers with different polymeric compositions. Various physical tests were performed for the formulated tablets such as weight variation, and thickness, hardness, and friability tests. The tablets were evaluated for uniformity of active ingredients by performing a pharmaceutical assay. The release of the model drug from the developed matrix tablets was performed in USP phosphate buffer of pH 6.8. The mechanism of drug release was studied by subjecting drug release data to various kinetic models.

MATERIALS AND METHODS

Chemicals

For the preparation of matrix tablets of various polymeric compositions, methocel E-5 (HPMC), HPC, and CMC sodium were used as polymers, respectively. Microcrystalline cellulose PH-200 was used as a bulking agent for the tablets. Talcum and magnesium stearate were used as lubricants, respectively. Deionized water and 0.1 N NaOH solution were used as solvents. Potassium dihydrogen phosphate, sodium chloride, and all other chemicals used were of analytical grade.

Preparation of the matrix tablets

Levosulpiride tablets were formulated and evaluated at Aims Pharmaceuticals (pvt) Ltd. Kahuta triangle industrial area, Islamabad, Pakistan, where all the tablet manufacturing equipment and testing instruments were available. Table 1 indicates the composition of all matrix formulations of the model drug (Levosulpiride). To formulate the tablets, the model drug, polymers, and excipients (except glidants and lubricants) were first passed individually from mesh #16 and then mixed
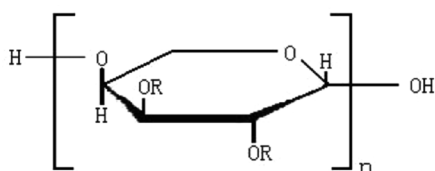

Figure 2. The Chemical structure of hydroxypropyl methyl cellulose

Table 1. Formulation Sheet of Levosulpiride sustained-release tablets

Formulation	Drug (Levosulpiride) (%)	Polymers		MCC (%)	Talc (%)	Mg stearate (%)
		Name	(%)			
F1	12.5	HPMC (K100LV)	50	35	1.25	1.25
F2	12.5	HPMC (K100LV)	65	20	1.25	1.25
F3	12.5	HPMC (K100LV)	75	10	1.25	1.25
F4	12.5	HPC (K100M)	50	35	1.25	1.25
F5	12.5	HPC (K100M)	65	20	1.25	1.25
F6	12.5	HPC (K100M)	75	10	1.25	1.25
F7	12.5	CMC sodium	50	35	1.25	1.25
F8	12.5	CMC sodium	65	20	1.25	1.25
F9	12.5	CMC sodium	75	10	1.25	1.25

MCC: Microcrystalline cellulose, HPMC: Hydroxypropyl methyl cellulose, HPC: Hydroxypropyl cellulose, CMC: Carboxy methyl cellulose, Mg: Magnesium
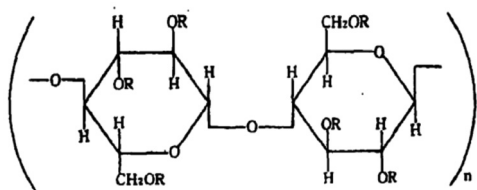
Figure 3. The chemical structure of hydroxypropyl cellulose

Figure 4. The chemical structure of Levosulpiride

for 15 min. The contents were mixed for a further 5 min after the addition of lubricants and glidants. The bulk was then compressed into tablets using a ZP-17 tablet compression machine (Shanghai Tianfeng, China). Before subjecting the bulk to the various physical tests, the micrometric properties of the powders were determined. The prepared formulations of the model drug were then evaluated for the various physical parameters.

Characterization

Micrometric properties of powders
Powder flow plays an important role in the manufacturing of a fine tablet. The flow properties of the powder blends were evaluated by determining the bulk density, tapped density, and angle of repose.

Bulk density
To measure the bulk density, a pre-sieved powder blend was carefully poured into a dry graduated cylinder without compaction and the weight and volume were measured. The unit of bulk density is g/mL and is given by

$$D_b = \frac{M}{V_0}$$

Where M represents the mass of powder and V_0 represents the bulk volume of the powder.

Tapped density
Tapped density was calculated by pouring a known mass of powder blend in a graduated cylinder placed on a mechanical tapping apparatus. The compact volume of the powder after tapping was measured. Tapped density is also expressed as g/mL and is given by

$$D_t = \frac{M}{V_t}$$

Where M represents the mass of powder and V_t is the tapped volume of the powder.

Angle of repose
The funnel method was adopted to measure the angle of repose. The powder was allowed to drop from the funnel to form a cone to a maximum height. The diameter of the heap (D) and height of the heap (h) was measured and the angle of repose (θ), which was calculated using the following formula:
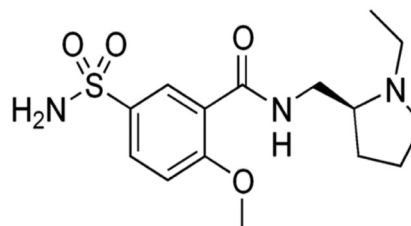
$$Tan\theta = \frac{h}{r}$$

$$\theta = Tan^{-1}\left(\frac{h}{r}\right)$$

Where, h is the height in cm, r is the radius, and θ is the angle of repose.

Weight variation
The weight variation of tablets was calculated as per the method described in the B.P using an electronic balance (Sartorius). The individual weights were then compared with the average weight for the determination of weight variation.

Hardness or crushing strength of tablets
The hardness test represents the structural integrity and the point at which the tablet breaks during storage, transportation, and handling before use. Moreover, the hardness of the tablet also affects the disintegration time. The hardness was measured using a digital hardness tester.

Thickness of tablets
Variation in tablet thickness may cause problems during counting and packaging. The thickness of tablets was determined using Vernier calipers.

Friability of tablets
Tablets from each formulation were selected randomly and weighed. The pre-weighed tablets were then placed in the plastic chamber of Roche friabilator. The friabilator allows the tablets to face a combined effect of abrasion and shock in a plastic chamber revolving at 25 rpm. After four min (100 revolutions), the tablets were removed, de-dusted, and weighed again. The following formula was used to calculate the friability of the tablets:

$$\frac{W_1 - W_2}{W_1} X100$$

Where W_1 is the initial weight of the tablets and W_2 is the final weight.

Content uniformity of tablets
The tablets were also evaluated for the content uniformity by randomly selecting a specific number of tablets from each formulation and weighed on a suitable tare container. The tablets were then powdered using a pestle and mortar and a solution of Levosulpiride was prepared in a 100-mL volumetric flask by dissolving the powder equivalent to 25

mg of Levosulpiride in 0.1 N NaOH. Further dilutions were made and the absorbance of the resultant solutions was measured against the standard at a wavelength of 214 nm using a UV-visible spectrophotometer.

Calculations

$$\%Assay = \frac{A_1}{A_2} \times 100$$

Where:

A_1 = Absorbance of sample

A_2 = Absorbance of working standard

In vitro drug release studies

A dissolution test was performed using dissolution test apparatus USP type II (Pharma test Germany) in phosphate buffer solution (pH 6.8) for all nine formulations of Levosulpiride. For this purpose, 900 mL of buffer solution was placed in each vessel of the dissolution test apparatus and the solution was allowed to reach a temperature of 37°C. A single tablet of Levosulpiride was placed in each vessel of the dissolution test apparatus and the apparatus was operated at a rate of 50 rpm. Five milliliters of the sample were collected from each vessel after defined intervals and was filtered and diluted with the dissolution medium. After each sampling, fresh dissolution medium was added to the vessels in order to maintain the volume of the dissolution medium.[24] The absorbance of the samples and standard were then measured using a UV-visible spectrophotometer.

Fourier-transform infrared (FTIR) spectroscopy

The structure and intermolecular interactions between components of the tablets were investigated using FTIR spectroscopy. The FTIR spectra of the tablets and individual components were recorded using a Thermo-Fischer Scientific Nicolet 6700 FTIR spectrometer at 8 cm^{-1} resolution averaging 256 scans. The spectra were collected over the 4000-400 cm^{-1} range.

Drug release kinetics

To evaluate the kinetics and *in vitro* drug release data, different mathematical models were used including the zero order rate equation, which describes the system where the drug release rate is independent of its concentration:[25]

$$Q = kt \qquad (1)$$

Where Q is amount of undissolved drug at time t, K is the zero order rate constant, and t is time.

The first order rate equation describes the system where the drug release rate is dependent on its concentration:[26]

$$LogC = LogC_0 - kt / 2.303 \qquad (2)$$

Where C_0 is the initial concentration of drug and K is the first order constant.

The Higuchi model is an invaluable framework that has been used to develop a number of drug delivery systems. A direct relationship between the amount of drug released from a matrix system and square root of time is established using the Higuchi model.[27] It is expressed in equational form as follows:

$$Q = K\sqrt{t} \qquad (3)$$

Where Q represents the percent of drug released in time; K is Higuchi's constant and t is the time.

The Hixson-Crowell cube root law describes drug release from systems where there is a change in surface area and diameter of particles or tablets.[28] The mathematical expression of this model is shown below:

$$Q_0^{1/3} - Q_t^{1/3} = K_{HC} t \qquad (4)$$

Q_0 is the initial amount of the drug in tablet, Q_t is the amount of drug released in time (t), and K_{HC} is the Hixson-Crowell rate constant.

A simple relationship to describe the release behavior of a drug from hydrophilic matrix systems was developed by Korsmeyer-Peppas, which is mathematically expressed as follows:

$$M_t / M_\alpha = K_{kp} t^n \qquad (5)$$

Where M_t / M_α is the fraction of drug released in time (t), K_{kp} is the rate constant incorporating the properties of macromolecular polymeric system and drug, and n is the release exponent used to characterize the transport mechanism.[29] The n value is used to describe various release mechanisms for cylindrical-shaped devices as shown in Table 2.

Table 2. Diffusion exponent and solute release mechanism for various systems	
Diffusion exponent	**Solute diffusion mechanism**
0.45	Fickian diffusion
0.45<n<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-ll transport
n>0.89	Super case-ll transport

RESULTS AND DISCUSSION

Flow properties of powders

The particle size of powders was found to be in the range of 760-890 μm, which resulted in free-flow properties of the powders. The data given in Table 3 show that the angle of repose for all formulation was <30 degrees, which clearly depicts that the granules had excellent flow characteristics.

Weight variation

The standard weight of Levosulpiride tablet was selected as 200 mg and the standard limit for weight variation was set as ± 5%. Twenty tablets from each formulation were selected and individual tablet weights were calculated. The results shown in Table 4 indicate that all results were within the specified range, which was also studied previously by Abdel-Rahman et al.[30]

Hardness of tablets

It is better considered that the hardness of uncoated tablets should not be less than 5 kg/cm^2. A minimum of 6 tablets should

be tested for hardness. Ten tablets from each formulation were selected and their hardness was calculated. According to Table 4, the average hardness of the tablets of all formulations was within the specified range, as previously described by Vueba et al.[13]

Thickness of tablets

Ten tablets from each formulation were taken and average thickness values were calculated. The usual thickness range of tablets weighing up to 250 mg is 3-4 mm. According to the results indicated in Table 4, the average thicknesses of the tablets of all formulations were within the specified limits.

Friability of tablets

The friability of tablets should be less than 1%. Twenty tablets from each formulation were selected at random and their percent friability was calculated. According to the results shown in Table 4, all results were within the specified limits.

Content uniformity of tablets

Twenty tablets from each formulation were selected randomly. Table 4 represents the content uniformity of each formulation and it is evident that each formulation was within the official limits i.e., 95-105%.

In vitro drug release studies

To study the *in vitro* drug release behavior from the polymer matrix in simulated intestinal medium, dissolution studies were conducted for all formulations. The dissolution test was performed using USP type II dissolution apparatus. The tablets were placed in 900 mL of phosphate buffer solution maintained at 37±1°C and the apparatus was operated at 50 rpm for 8 hrs. To study the effect of the polymer on drug release, the polymer-drug ratio was altered. Formulations F1, F2, and F3 contained HPMC, F4, F5, and F6 contained HPC, and F7, F8, and F9 contained CMC sodium in an increasing order of polymer drug ratio. The percentage of drug release from the matrix tablets as shown in Table 5, which indicates that the drug release from the formulations reduced as the polymer ratio increased, irrespective of the type of polymer used. The data also show that Levosulpiride release from the matrix tablet was sustained over an extended period of time at pH 6.8 and the sequence of retarding the drug release was found as CMC sodium ⟩ HPC ⟩ HPMC. Among the three polymers, CMC sodium proved to be the best retarding material and formulation 9 was found to be the best one. Figure 5, 6, 7 indicates the individual *in vitro* drug release profile of all the developed matrix tablet samples. Figure 8 represents the cumulative percentage release of all the formulations.

FTIR spectroscopy

The FTIR spectra of pure Levosulpiride, CMC sodium, and their blends are given in Figure 9, 10, and 11, respectively. The FTIR spectrum of Levosulpiride demonstrates sharp transmittance bands for (C-H) at 2810 cm⁻¹, which also appears in the final spectrum. The characteristic (−OH/−NH) bands in Levosulpiride at 3124 cm⁻¹ and 3367 cm⁻¹ also shifted to short and broader peaks, which depicts the involvement of these groups in interfacial H-bonding between the components.

Table 3. Evaluation of powder flow for Levosulpiride sustained-release tablets

S. no	Formulation	Angle of repose	Bulk density (g/mL)	Tapped density (g/mL)
1	F1	29.01±0.18	0.700±0.02	0.830±0.001
2	F2	28.76±0.09	0.730±0.05	0.850±0.003
3	F3	28.13±0.18	0.718±0.01	0.865±0.002
4	F4	29.22±0.18	0.747±0.04	0.889±0.006
5	F5	25.01±0.18	0.710±0.02	0.836±0.001
6	F6	24.76±0.09	0.735±0.05	0.854±0.003
7	F7	29.13±0.18	0.713±0.01	0.869±0.002
8	F8	28.22±0.18	0.765±0.04	0.881±0.006
9	F9	27.01±0.18	0.701±0.02	0.840±0.001

All data are reported as mean±SD, n=3 per experiment

Table 4. Evaluation of Levosulpiride sustained-release tablets

Formulation	Average weight (mg)	Average hardness (kg)	Average thickness (mm)	Friability (%)	Assay (%)
F1	205	6.5	3.40	0.52	97
F2	201	6.4	3.56	0.74	101
F3	200	6.3	3.60	0.46	102
F4	198.9	6.2	3.90	0.28	95
F5	202	7.0	3.80	0.19	98
F6	199.6	6.9	3.80	0.48	102
F7	199	6.8	3.62	0.67	97
F8	202	7.0	3.62	0.43	103
F9	200	6.9	3.62	0.22	98

All data are reported as mean±SD, n=3 per experiment

The other important contributions from Levosulpiride are the presence of an amide I band corresponding to (C=O) vibration of the acetyl group at ~1623 cm^{-1} and (C–N) stretching vibration at ~1060 cm^{-1}, which can also be seen in CMC sodium. FTIR spectroscopy revealed that no chemical interaction occurred between the components.

Drug release kinetics

Using zero order, first order kinetic models, the Higuchi, Hixon–Crowell, and Korsmeyer–Peppas models, drug-release kinetics were investigated. The values of drug-release constant (k) and regression coefficient (r) were obtained.

To examine the drug release mechanism, the data obtained from all nine formulations was fitted into the various kinetic models. The results obtained from the kinetic models are presented cumulatively in Table 6. It is evident from the data that the formulations released the drug according to Higuchi's pattern. The "n" value for all formulations was found to be greater than 0.5, which according to the Peppas model, approximates the non-Fickian diffusion mechanism, as shown in Table 6.

Figures 12, 13, 14 show the graphs for the Higuchi model for formulations 07-09.
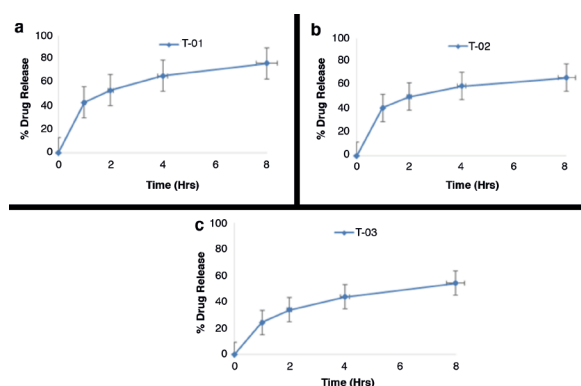
CONCLUSIONS

SR tablets of Levosulpiride were prepared successfully using polymers such as HPMC, HPC, and CMC sodium in varying concentrations. The particle size and drift behavior of the granules were found to be in accordance with the official standards. Direct compression method was selected on the basis of Good compressibility index of the granules. The physical properties of compressed tablets like thickness, hardness, weight variation and friability were in compliance with the official limits. Free-flowing powder facilitates the formation of tablets with ideal properties. The drug release was primarily controlled by the type and concentration of polymers and a slight change in polymer concentration resulted in altered drug release. On the basis of these results, it can be concluded that the drug release could be further prolonged if the polymers are used in combination because of their possible interaction and subsequent cross-linking. The kinetic model that best fits to the release data was found as the Higuchi's equation, followed by zero order with non-Fickian behavior over an 8-hr period. The objective of the study was met through the formulation of a novel SR formulation of Levosulpiride, which will help to
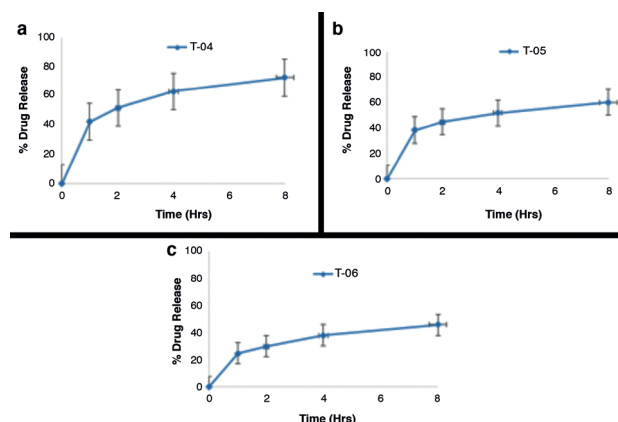

Figure 5. *In vitro* drug release profile of formulations a) T-01 b) T-02 c) T-03 after 8 hours in phosphate buffer solution of pH 6.8 at 37°C

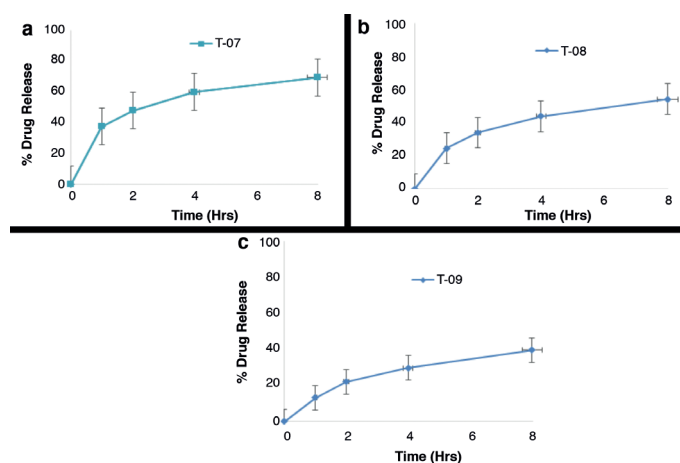**Figure 6.** *In vitro* drug release profile of formulations a) T-04 b) T-05 c) T-06 after 8 hours in phosphate buffer solution of pH 6.8 at 37°C

Table 5. *In vitro* drug release data from compressed matrix tablets of Levosulpiride

S. No	Formulation	Percentage release of Levosulpiride			
		1st hour	2nd hour	4th hour	8th hour
1	F1	43.22%	53.52%	65.96%	76.44%
2	F2	41.02%	50.27%	59.39%	66.68%
3	F3	24.64%	34.18%	44.14%	54.40%
4	F4	42.28%	57.61%	62.98%	72.55%
5	F5	38.26%	44.81%	51.91%	60.41%
6	F6	24.53%	29.79%	37.90%	45.82%
7	F7	37.48%	47.81%	59.90%	69.42%
8	F8	26.95%	36.93%	46.56%	56.95%
9	F9	13.18%	21.99%	29.71%	39.66%

All data are reported as mean±SD, n=3 per experiment

Table 6. Data showing *in vitro* release kinetics of various formulations of Levosulpiride in buffer pH 6.8

| Formulation	Zero-order		First-order		Higuchi		Hixon-Crowel		Korsmeyer-Peppas		Result
	R^2	K	R^2	K	R^2	K	R^2	K	R^2	n	
F1	0.680	7.705	0.865	-0.160	0.976	18.04	0.887	0.097	0.993	0.864	AM
F2	0.620	6.512	0.764	-0.116	0.989	13.74	0.859	0.078	0.994	0.881	AM
F3	0.782	5.817	0.875	-0.088	0.981	16.01	0.884	0.115	0.991	0.871	AM
F4	0.664	7.237	0.834	-0.140	0.976	16.43	0.889	0.091	0.994	0.881	AM
F5	0.620	5.815	0.748	-0.095	0.991	11.94	0.927	0.074	0.990	0.876	AM
F6	0.729	4.703	0.748	-0.095	0.992	11.72	0.927	0.091	0.993	0.864	AM
F7	0.699	7.105	0.849	-0.131	0.969	17.31	0.872	0.100	0.990	0.881	AM
F8	0.761	6.005	0.864	-0.093	0.979	16.03	0.882	0.110	0.991	0.871	AM
F9	0.870	4.491	0.918	-0.058	0.998	14.09	0.872	0.134	0.993	0.881	AM

AM: Anomalous

Figure 7. *In vitro* drug release profile of formulations a) T-07 b) T-08 c) T-09 after 8 hours in phosphate buffer solution of pH 6.8 at 37°C
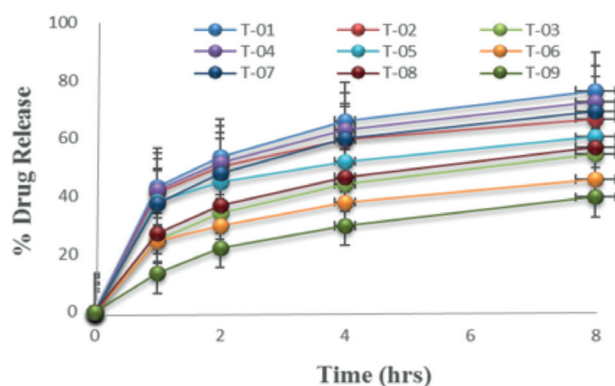
Figure 8. *In vitro* drug release profile of Levosulpiride sustained-release tablets of all the prepared 09 samples after 8 hrs in phosphate buffer solution of pH 6.8 at 37°C
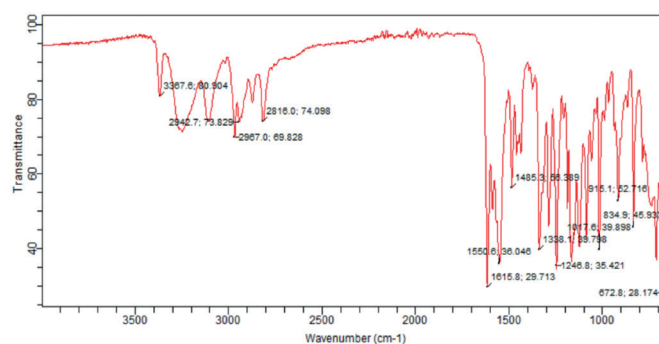
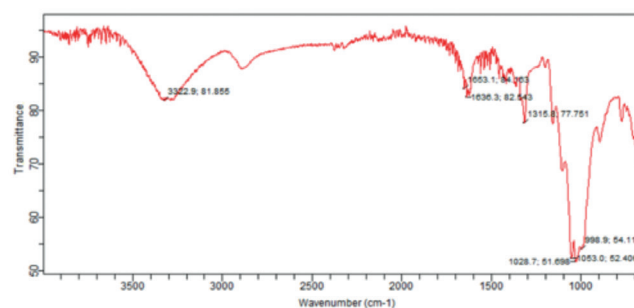**Figure 9.** Fourier-transform infrared-spectrum of pure Levosulpiride

Figure 10. Fourier-transform infrared spectrum of carboxy methyl cellulose sodium

reduce dosing frequency, plasma drug level fluctuations, dose-related adverse effects and improve patient compliance. These prepared tablets can be evaluated in the future for their stability studies and *in vivo* behavior and to develop an *in vitro-in vivo* correlation.
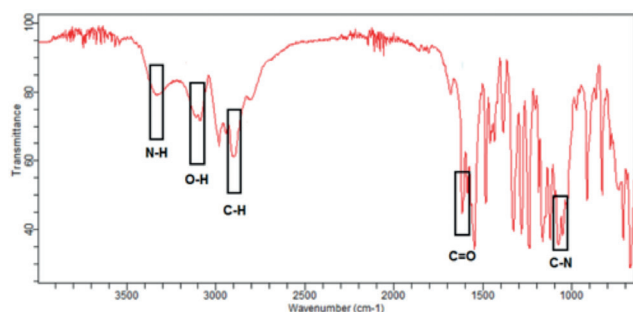
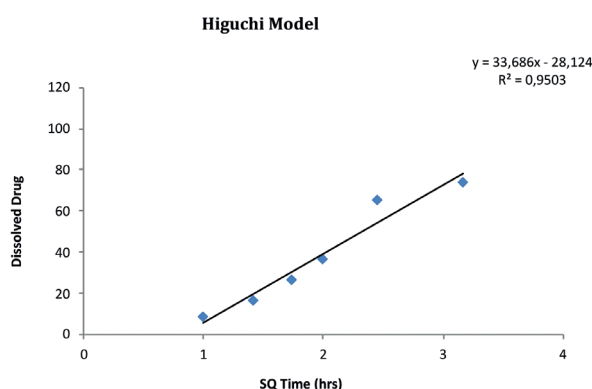**Figure 11.** Fourier-transform infrared spectra of Levosulpiride and carboxy methyl cellulose sodium

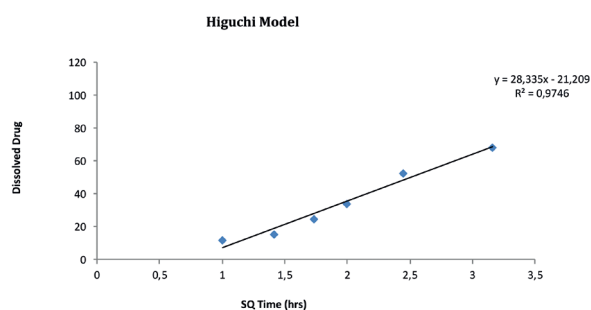
Figure 12. Graph of Higuchi model for formulation T-07

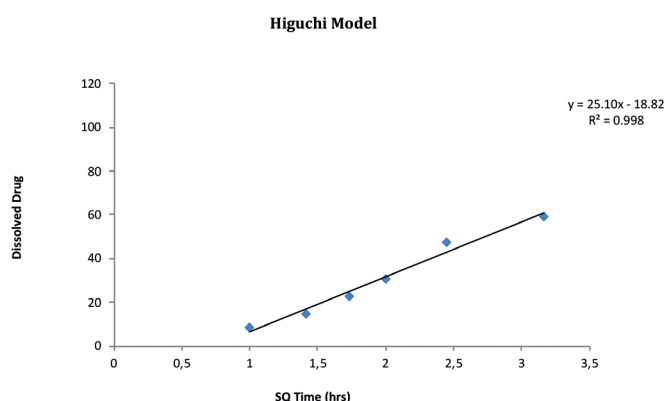**Figure 13.** Graph of Higuchi model for formulation T-08

Figure 14. Graph of Higuchi model for formulation T-09

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