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FORMULATION AND EVALUATION OF MATRIX TABLETS OF VERAPAMIL HYDROCHLORIDE BY SOLID DISPERSION METHOD

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ABSTRACT

The aim of the study was to improve the solubility and dissolution rate of the drug Verapamil HCL using solid-dispersion-Sustained release matrix tablets by direct compression method. Solid dispersions were prepared by solvent evaporation technique using PEG 6000 poloxamer 188 and Urea as carriers. The solid dispersions were characterized by using FTIR and confirmed that no chemical interaction during entrapment process. The prepared solid dispersions were formulated in matrix tablets evaluated for pre-compression and post-compression parameters. The post compression parameters were evaluated for hardness, friability, weight variation and drug content which were within the acceptable official limits. The drug content was found to be high and uniformly distributed in all formulations. It was shown that with the developed formulations, the release and dissolution of drug from the tablets can be increased by formulating it as solid dispersion tablets. It was concluded that development of sustained release solid-dispersion tablets using poloxamer 188 [97%] with HPMC K4m results highest increase in dissolution rate and optimum rate of drug and reduced crystallinity of Verapamil HCL can account for the faster dissolution of the released drug from the polymer matrix.

KEYWORDS: Verapamil Hcl, Poloxamer-188, solid dispersion, solvent evaporation method, Dissolution, SD-SR.

1. INTRODUCTION

Verapamil hydrochloride is a calcium channel blocker and a class IV antiarrhythmic agent used in the control of supraventricular arrhythmias and in the management of angina pectoris,

hypertension and myocardial infraction.[1] VPH has short biological half-life of 4-5 hours and hence it is necessary to administer frequently due to which VPH can be considered as a potential candidate for a design of sustained release dosage forms. Hence, sustained release tablets or VPH is formulated which in turns prolong its duration of action and reduction of usage frequency.[2]

1.1. Solid dispersion

Solid dispersion is another approach widely used for the enhancement of solubility of poorly water soluble drugs. The concept of solid dispersion was introduced by Sekiguchi and Obi. In solid dispersion method the drug is dispersed in extremely fine state in an inert water-soluble carrier in solid state. A number of freely water-soluble materials such as citric acid, bile acids, sterols and related compounds and polymers like Polyvinylpyrrolidone and Polyethylene glycols were used as carriers for solid dispersions. By this approach the dissolution rate and bioavailability of poorly soluble drug can be increased.[3] Solid dispersion [SD] is one of the commonly used methods to improve the solubility, dissolution characteristics and bioavailability of the poorly soluble drug. It involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or meltingsolvent method. The technique has been used for a wide variety of poorly aqueous soluble drugs.[4]

1.2. Matrix Tablets

Matrix tablet has given new break, through for novel drug delivery system in the field of pharmaceutical technology.[5] It's the type of tablet which is designed such that it releases itscontents regarding first order kinetics or zero order kinetics due to special arrangement and combination of hydrophobic and hydrophilic polymers as an excipient to form a matrix,[6] example of such a matrix tablets are, controlled release tablet, sustained released tablet. These all come under the category of modified release tablet.Matrix systems are widely used for the purpose of sustained release. It is the release system which prolongs and controls the release of the drug that is dissolved or dispersed. In fact, a matrix is defined as a well-mixed composite of one or more drugs with gelling agent i.e. hydrophilic polymers. In this method therapeutically effective concentration can be achieved in the systemic circulation over an extended period of time, thus achieving better compliance of patients. Numerous SR oral dosage forms such as membrane controlled system, matrices with water soluble/insoluble

polymers or waxes and osmotic systems have been developed, intense research has recently focused on the designation of SR systems for poorly water soluble drugs.[7]

1.3. Sustained Release Tablets

During the last two decades there has been a remarkable increase interest in sustained release of drug delivery systems. This has been due to various factors like the prohibitive cost of developing new drug entities, expiration of existing international patients, discovery of new polymeric materials suitable for prolonging the drug release, and improvement in the therapeutic efficacy and safety achieved by these delivery systems.[8]

2. MATERIALS AND METHODS

2.1 Materials

Verapamil HCL, HPMC K4m and HPMC K100m were procured from yarrow chem. Pvt.Ltd Mumbai, Poloxamer 188, PEG 6000, Urea, Magnesium Stearate and Talc were Procured from SD Fine chem Ltd.

2.2 Methods

2.2.1. Compatibility study using FT-IR

FT-IR spectra of the prepared formulations were taken and compared with the spectrum of pure drug the characteristic peaks of drug were checked in the formulation spectra.

2.2.2. Preparation of solid dispersions of Verapamil HCL

Solid dispersion is one of the most commonly used technique to improve the solubility of water insoluble drugs which in turn improves the bioavailability. Solid dispersions are prepared by solvent evaporation method. In solvent evaporation method, both drug and the carrier are dissolved in a common solvent, and the solvent is evaporated to get solid dispersions.

The preliminary solubility study indicated that carriers like PEG 6000, poloxamer 188 and Urea can be tried in preparation of solid dispersions for solubility and dissolution enhancement. Hence solid dispersions are prepared in order to improve the solubility using carriers like PEG 6000 poloxamer and urea.

2.2.3. Preparation of physical mixtures

Co-ground the solid dispersions of verapamil HCL and varying amounts of carriers until a homogeneous mixture is obtained and sieved in #44 and pulverized and stored in desiccators at room temperature.

2.2.4. Solvent evaporation method

In this method, the carriers such as PEG 6000, Poloxamer and Urea are used. The drug to polymer ratio used is 1:1. In this method, drug and carrier are dissolved in methanol with constant stirring. Solution is evaporated under low pressure to get the solid dispersions. After complete evaporation of the solvent the resulting residue is further dried in desiccator over anhydrous calcium chloride. The dried solid mass is pulverized in a mortar and pestle and then passed through sieve #44 and stored in desiccator at room temperature.

2.2.5. Formulation development of Verapamil HCL SD-SR tablets

The sustained release tablets were prepared by direct compression methods. The solid dispersion containing matrix tablets were prepared by adding equivalent weight of the drug of solid dispersion and the weight of all the other ingredients during weighing are checked. For direct compression the sifted powders are mixed thoroughly with all other excipients and compressed.

Compression Process

Compression is defined as the reduction in volume of a powder owing to the application of forces. Because of the increased proximity of particle surfaces accomplished during compression, bonds are formed between particles which provide coherence to the powder i.e. compact is formed.

The granules prepared were subjected to compression. Compression was performed by filling the die cavity with the weighed quantity of powder for compression. The hardness maintained was 6kg/cm^2. The compressed tablets were taken and evaluated for various parameters.

2.3. Evaluation of Verapamil HCL solid dispersions and SD –SR tablets.

2.3.1. Calculation of percentage practical yield of solid dispersion

$$\%\ \text{practical yield} = \frac{\text{practical mass (SolidDispersion)}}{\text{theoretical mass}} \times\ 100$$

2.3.2. Drug content estimation

Solid dispersions of Verapamil Hcl equivalent to 150 mg are weighed and dissolved in little amount of phosphate buffer [6.8pH] in volumetric flask and volume is made upto 100 ml with the buffer pH 6.8 and subsequent dilutions are made and absorbance is measured at 278 nm and drug content is calculated using standard curve. Each test is performed in triplicate.

$$\% \text{ drug content} = \frac{\text{actual drug content in solid dispersion}}{\text{theoretical amount of drug in solid dispersion}} \times 100$$

2.3.3. In-vitro dissolution studies

Dissolution studies for solid dispersion

Procedure

The dissolution testing is carried out at a temperature of 37°C at 100 RPM in 900 ml 1.2pH acidic HCl buffer and 6.8pH phosphatebuffer as a dissolution medium using USP dissolution test apparatus type II. One capsule [containing pure drug/ physical mixture/Solid Dispersion equivalent to 150 mg] is placed in the basket, basket is then immersed in dissolution medium. A specified volume of aliquot is withdrawn at specified time intervals, filtered through 0.45µ filter and the concentration of drug is determined spectrophotometrically at 278 nm against blank. An equal volume of fresh dissolution medium is replaced immediately. The cumulative percentage release of Verapamil HCL iscalculated. The studies are carried out in triplicate. The cumulative percentage release v/s time [minutes] are plotted and the dissolution profile of Verapamil HCL pure drug and solid dispersionsare compared.

2.4. Evaluation of Verapamil HCL SD sustained release tablets

2.4.1. Angle of repose

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of Verapamil HCL granules were passed through a funnel from a particular height [2cm] onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula. Angle of repose ø = tan-1[h/r] Where, h – Height of the pile in cm, r – Radius of the pile.

2.4.2. Bulk density [Db]

The bulk density of the formulated granules was evaluated using a bulk density apparatus. It is the ratio of total mass of powder to the bulk volume of powder. It was measured by pouring the weighed powder into a graduated measuring cylinder and the volume was noted. It is expressed in gm/ml and is given by

Db = M/Vb

Where, D**b** – bulk density M - Mass of the powder, Vb – Bulk volume of the powder.

2.4.3. Tapped density [DT]

It is the ratio of total mass of powder to the tapped volume of powder. The tapped volume was measured by tapping the powder to constant volume. It is expressed in gram/ml and is given by

DT=M/Vt

Where, D**t –** tapped density M - Mass of the powder Vt – Tapped volume of the powder.

2.4.4. Hausner's ratio

Hausner's ratio indicates the flow properties of the powder and is measured by the ratio of tapped density to the bulk density.

Hausner's Ratio = Tapped density/Bulk density

2.4.5. Carr's index

Compressibility index is an important measure that can be obtained from the bulk and tapped densities. In theory, the less compressible a material the more flowable it is. A material having values of less than 20 to 30% is defined as the free flowing material.

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

2.4.6. Hardness

The prepared tablets were subjected to hardness test. It was carried out by using hardness tester and expressed in kg/cm^2.

2.4.7. Friability [F]

The friability was determined using Roche friabilator and expressed in percentage [%]. 20 tablets from each batch were weighed separately [Winitial] and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed [Wfinal] and the percentage friability was calculated for each batch by using the following formula.

$$\% \text{ friability} = \frac{\text{Initial weight} - \text{final weight}}{\text{Initial weight}} \times 100$$

2.4.8. Weight variation test

20 tablets were selected randomly, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was

calculated. The test requirements are met; if not more than two of the individual weights deviate from the average weight by not more than existing 5%.

2.4.9. *In vitro* drug release studies

The *in vitro* dissolution studies were carried out for the formulations using USP apparatus type II [Paddle type] for 12 hours. The samples were measured by UV Spectrophotometer at 278 nm against a blank. The absorbance was recorded and was plotted versus time.

***In-vitro* dissolution in 0.1N HCL**

Dissolution apparatus: USP type – II [Paddle type]

Rpm: 100

Medium: 900, 1.2 pH HCL

Temperature: 37 °C ± 0.5°C

Sampling interval: 1 hour, 2 hours respectively**.**

Sample withdrawn: 5ml.

***In-vitro* dissolution in pH 6.8 phosphate buffer:**

Dissolution apparatus: USP type – II [Paddle type]

Rpm: 100

Medium: 900ml,pH 6.8 Phosphate Buffer

Temperature: 37 °C ± 0.5°C

Sampling interval: 3, 4, 5, 6, 7, 8, 9, 10, 11, 12 hours respectively.

Sample withdrawn: 5ml.

2.5. Release Kinetic Models

Data obtained from the *in vitro* release studies were fitted to various kinetic equations such as zero order, first order, Higuchi model and Korsemeyer- Peppas model.

a] Zero order kinetics

When the data is plotted as cumulative % drug release versus time, if the plot is linear then the data obeys zero-order release Kinetics, with a slope equal to K^0.

Zero order release would be predicted by the following equation

$$\mathbf{A_t = A_0 - K_0 t}$$

Where, A_t= Drug release at time‘t’.

A_0= Initial drug concentration.

K_0=Zero-order rate constant [hr^{-1}].

b] First order Kinetics

When the data is plotted as log cumulative % drug remaining versus time yields a straight line, indicating that the release follows first order kinetics. The constant 'K' can be obtained by multiplying 2.303 with the slope values.

First order release would be predicted by the following equation:-

$\text{Log } C = \log C_0 - K_t / 2.303$

Where,C = Amount of drug remained at time't'.

C_0 = Initial concentration of drug.

K = First-order rate constant [hr^{-1}].

c] Higuchi's model

When the data is plotted as cumulative drug release versus square root of time, yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to 'K' [Higuchi's 1963].

Drug release from the formulation by diffusion has been described by following Higuchi's classical diffusion equation:

$Q = [D_\varepsilon / \varepsilon [2A - \varepsilon C_S] C_S t]^{1/2}$

Where,Q = Amount of drug released at time't'.

D = Diffusion co-efficient of the drug in the matrix.

A = Total amount of drug in unit volume of matrix.

C_S = Solubility of the drug in the matrix.

ε = Porosity of the matrix.

t = Tortuosity.

d] Korsmeyer equation/ Peppa's model

When the data is plotted as log of drug released versus time, yields a straight line with a slope equal to 'n' and the 'K' can be obtained from y- intercept. To study the mechanism of drug release, the release data were also fitted to the well – known exponential equation [Korsmeyer equation/ Peppa's law equation], which is often used to describe the drug release behavior from polymeric systems.

$M_t / M_a = Kt^n$

Where, M_t / M_a = the fraction of drug released at time't'.

K = Constant incorporating the structural and geometrical characteristics of the drug/polymer.

n = Diffusion exponent related to the mechanism of the release.

Above equation can be simplified by applying log on both sides,

Log M_t / M_a = Log K + n log t

For Fickian release 'n' = 0.5 while for anomalous [non- Fickian] transport 'n' ranges between 0.5 and 1.0.

2.6. Stability conditions

The reason of stability testing is to provide evidence on how the quality of drug formulation varies with time under the influence various environmental conditions such as temperature, humidity, light. From this study recommended storage conditions humidity, light, re-test periods and self-life of the drug can be established. The selected formulations were subjected for three month for stability studyas per ICH guidelines**.**In the study, the developed formulation of sustained release tablets of Verapamil Hcl was subjected to stability studies. The conditions maintained throughout the study were 40°C±2°C/75RH±5%RH. These conditions were maintained up to three months and the parameters like hardness and *in-vitro* dissolution study of the formulation were evaluation.

3. RESULTS AND DISCUSSION

3.1. Selection of drug

The purpose of the present work was to increase the solubility of verapamil hcl by solid dispersion and formulate it as sustained release matrix tablets. The solid dispersions were prepared by solvent evaporation method and followed by formulation as sustained release by direct compression or wet granulation. The polymers used for increasing the solubility are PEG-6000 and Pol-188 and the polymers used for sustaining the release of drug from the tablet are HPMC-K_4M, HPMC K_{100}M, Guar gum, Sodium CMC. As the API is a poorly soluble compound in aqueous fluids, so the attempt is made to increase the solubility and formulate it as sustained matrix tablets. Being a BCS Class II drug, it often shows dissolution rate-limited oral absorption and high variability in pharmacological effects. Therefore, improvement in its solubility and dissolution rate may lead to enhancement in drug availability.

3.2. Solubility of drug

Solubility of verapamil hcl was found to be 4.47mg/L indicating it is practically poorly soluble in water.

3.3. Compatibility study

FTIR is carried out to test the possible intermolecular interaction between drug and excipient. Verapamil Hcl powder exhibited sharp peaks in the FTIR spectrum indicating that there was no interaction between drug and polymers.

3.4. Analytical method for standard curve of verapamil Hcl

Standard graph of Verapamil hcl was prepared by scanning the samples in UV spectrophotometer between 200 to 400 nm. A sharp peak was observed at 278nm by using 6.8P^{H} Phosphate buffer in water and the values are shown [table no 3] and graph in [Fig no 1]

3.5. Preliminary solubility studies

The preliminary solubility study showed that carriers like Urea, Polaxomer-188 and PEG-6000 gave highest solubility, but with urea the formulations obtained showed more moisture retaining and cannot be formulated as tablets. So the SD preparations were tried only with PEG-6000 and Poloxamer-188 for solubility and dissolution enhancement.

3.6. Preparation of solid dispersion and physical mixture

The solid dispersions and physical mixtures of verapamil hcl were prepared by using PEG-6000, Polaxomer-188 by solvent evaporation method, in the ratio of drug**:** carrier 1:1.

3.7. Formulation of sustained release matrix tablets

The solid dispersion containing matrix tablets are prepared by using the HPMC-K_4M, HPMC-K_{100}M, Guar gum and Sodium CMC. The tablets were prepared by direct compression method. The matrix tablets were prepared by the method described in the methodology section and subjected to tablet properties like thickness, hardness, friability, weight variation and drug content and In-vitro drug release study.

3.8. Evaluation of prepared SD's

3.8.1.*In-vitro* dissolution studies for pure drug and solid dispersions

The in-vitro dissolution studies of pure drug, SD-physical mixture and SD's, were carried out at 37°C at 100 rpm in 900 ml of 1.2pH HCl buffer and 6.8pH buffer, dissolution test apparatus employing basket type [method I]. The samples withdrawn were analyzed by using UV spectrophotometer at 278 nm. The cumulative percentage release v/s time were plotted.

The results of the dissolution studies carried out on of puredrug [150 mg], SD-physical mixture and SD's are shown in the table no-4, 5. The dissolution release profiles are given in fig no-4, 5.

The cumulative percentage release of pure drug after 60 minutes is 26±0.61% in acid media [1.2pH] and 56±0.8% in basic media [6.8pH] buffers. Physical mixture of verapamil Hclwith carriers showed enhancement in the dissolution rate as compared to pure drug but they exhibited lower rate of dissolution compared to solid dispersions.

From the dissolution study it was found that solid dispersions of verapamil Hcl showed more solublity of drug for the formulations [SD-1 and SD-2] prepared by solvent evaporation when compared to Physical mixture [SD-3 and SD-4] and pure drug [SD-5] formulations. In comparison for the formulations prepared by solvent evaporation technique the formulation with PEG-6000 [SD-1] showed more drug dissolution in 1.2pH acid media [83±0.15%] when compared to Pol-188 [62±0.75%] which is very less. Where as in the 6.8pH basic media POL-188 [SD-2] showed nearly 100% of drug dissolution [97±0.04%] when compared with PEG-6000 [SD-1] which has lesser rate of dissolution [87±0.23%]. This might be due to the higher solubility of PEG in acid media and POL-188 in basic media which increases the wettability of the drug.

3.9. Evaluation of prepared SD-SR tablets

3.9.1. Pre compression and post compression parameters

The pre-compression and post compression parameters for the prepared tablet formulations were evaluated and all the parameters lied within the range, and the assay values for the formulated SD sustained release formulation were found to be in the range of 100 ±5 % and the results are given in the table no 6, 7 and 8. All the results indicated that the process employed to prepare SD-SR tablets in this study are capable of producing formulations with uniform drug content.

So, these four polymers [HPMC-K_4M, HPMC-K_{100}M Guar gum and Sodium CMC] are considered for the formulation of SD-SR tablets. All the SD-SR formulations showed more dissolution of drug from their matrix and also showed concentration independent release profile. So, these formulations showed a better release profiles and order of release.

Among these FS-6 nearly showed 100% release and followed the concentration independent release [n=1.3153]. As soon as the SR polymer matrix releases the SD into the aqueous fluids surrounding it, a hydrophilic carrier dissolves and insoluble drug is exposed to dissolution medium in the form of very fine particles, leading to rapid dissolution. In addition, the greater hydrophilicity of POL-188 and increased wettability of the drug might contribute to these results led to the conclusion that solid oral dosage forms of verapamil Hcl with POL-188 and HPMC-K_4M can be formulated as a SD-SR with a high dissolution rate, faster onset of action, and improved bioavailability.

Among the three polymers used in the preparation of SD-SR, HPMC-K_4M gave the best optimum and concentration independent release of drug.

The best formulation of SD-SR [FS-6] with POL-188 and HPMC-K_4M was prepared. It was found that the dissolution rate was optimum and higher in SD-SR tablets.

3.9.2. Stability studies

Further, the optimized formulation was subjected to stability studies at 40^0C/75% RH. It has shown no any significant change in physical appearance and drug release profile indicating that formulation FS-6 was stable. Finally from the results, batch FS-6 was considered to be an optimized batch in which all the parameters of the formulation are satisfactory after three months stability was shown in [table 11]

4. CONCLUSION

Verapamil Hcl SD-SR tablets were prepared by direct compression method. The release and dissolution of drug from the tablets can be increased by formulating it as solid dispersion tablets. The formulation FS-6 consists of verapamil Hcl [150mg], Poloxamer-188 [150mg], HPMC-K4M [75mg], Lactose [51mg], magnesium stearate [12mg] and talc [12mg] was selected as the optimized formulation with sufficient rate of release and *in-vitro* dissolution. Various physicochemical parameters tested for this formulation have shown good results. It was concluded that development of sustained release-solid dispersion tablets not only releases the drug for a sustained period of time but also increases the dissolution rate of Verapamil Hcl. In addition, these formulations reduce the need of frequent administration and enhance patient compliance.

5. TABLES AND FIGURES

Table 1: Formulation Table of SD with different Polymers

Sl.no	Name of the ingredient	SE method [Weight in mg]			Physical mixture [Weight in mg]		
		SD.1	SD.2	SD.3	SD.4	SD.5	SD.6
1	Drug	150	150	150	150	150	150
2	PEG-6000	150	-	-	-	150	-
3	Poloxamer 188	-	150	-	-	-	150
4	Urea	-	-	150	150	-	-

Table 2: Formulation development of Verapamil HCL sustained release tablets with solid dispersions.

Sl. No	Name of the ingredient	Formulation code								
		FS 1	FS 2	FS 3	FS 4	FS 5	FS 6	FS 7	FS 8	FS 9
1	Drug	225	225	225	225	225	225	225	225	225
2	PEG-6000	150	150	150	150	-	-	-	-	-
3	Polaxomer-188	-	-	-	-	150	150	150	150	150
4	Lactose	51	51	51	51	51	51	51	51	51
5	Guar Gum	75	-	-	-	75	-	-	-	-
6	HPMC-K4m	-	75	-	-	-	75	-	-	30
7	HPMC-K15m	-	-	75	-	-	-	75	-	35
8	Sodium CMC	-	-	-	75	-	-	-	75	-
9	Magnesium stearate	12	12	12	12	12	12	12	12	12
10	Talc	12	12	12	12	12	12	12	12	12
Total tablet weight		450	450	450	450	450	450	450	450	450

Table 3: Standard calibration curve for Verapamil Hcl in 6.8 pH phosphate buffer.

Sl no	Concentration[µg/ml]	Absorbance*
1	0	0
2	5	0.068
3	10	0.132
4	15	0.202
5	20	0.264
6	25	0.34
7	30	0.409

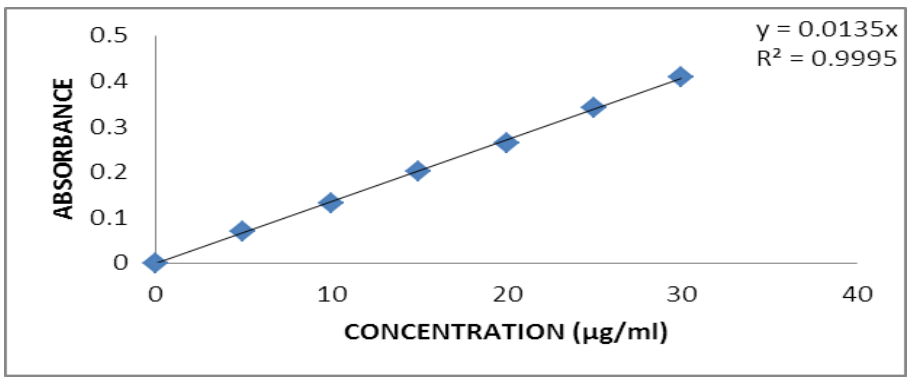

Fig 1: Standard graph of Verapamil Hcl.

Compatibility studies of Verapamil Hcl

FT-IR

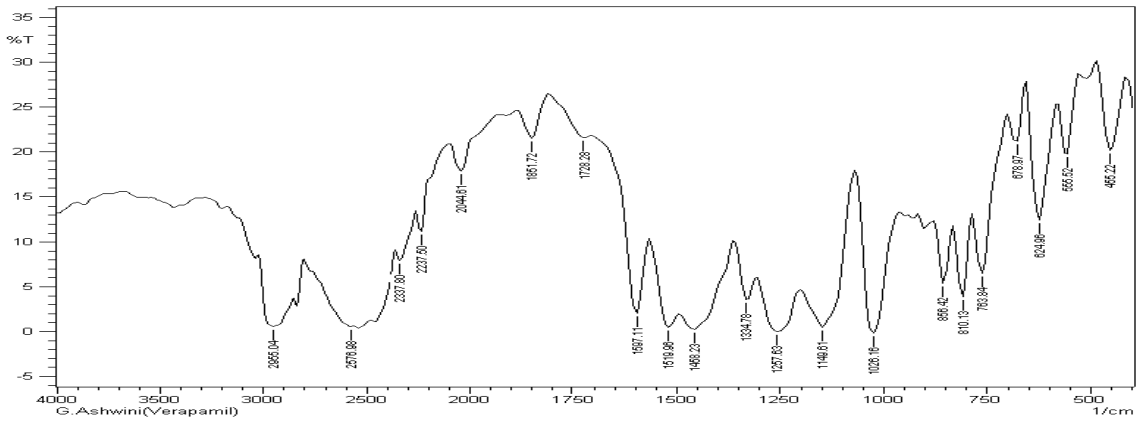

Fig 2:FT-IR of Verapamil Hcl.

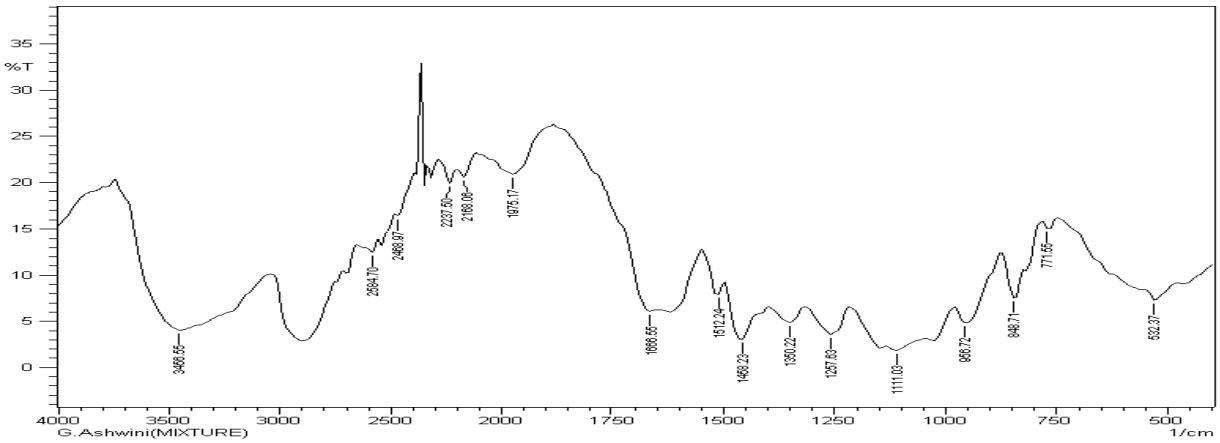

Fig 3: FT-IR of Verapamil Hcl

Table 4: In vitro release studies of Formulations SD 1-A to SD 5-A [acid media]

Sl.no	Time [mins]	SD 1	SD 2	SD 3	SD 4	SD 5 [pure drug]
0	0	0	0	0	0	0
1	5	36±0.84	27±0.20	23±0.59	17±0.55	11±0.28
2	10	48±0.8	42±0.52	28±0.97	27±0.3	14±0.62
3	15	60±0.4	49±0.12	34±0.56	31±0.76	19±0.85
4	20	67±0.34	51±0.45	38±0.31	34±0.22	21±0.27
5	30	79±0.88	54±0.55	40±0.21	41±0.11	22±0.42
6	45	81±0.25	59±0.10	43±0.61	43±0.02	24±0.41
7	60	83±0.15	62±0.75	47±0.69	47±0.47	26±0.61

Table 5: In vitro release studies of Formulations SD 1-B to SD 5-B [base media]

Sl.no	Time [mins]	SD 1	SD 2	SD 3	SD 4	SD 5 [pure drug]
0	0	0	0	0	0	0

1	5	23±0.82	15±0.5	18±.65	25±0.73	7±0.97
2	10	42±0.72	22±0.27	31±.68	36±0.66	16±0.39
3	15	50±0.31	40±0.71	37±.47	42±0.76	23±0.56
4	20	59±0.97	50±0.44	46±.33	50±0.81	27±0.96
5	30	75±0.19	71±0.95	49±.50	52±0.32	41±0.21
6	45	81±0.67	93±0.36	54±.55	55±0.87	47±0.84
7	60	87±0.23	99±0.04	60±.61	63±0.60	56±0.08

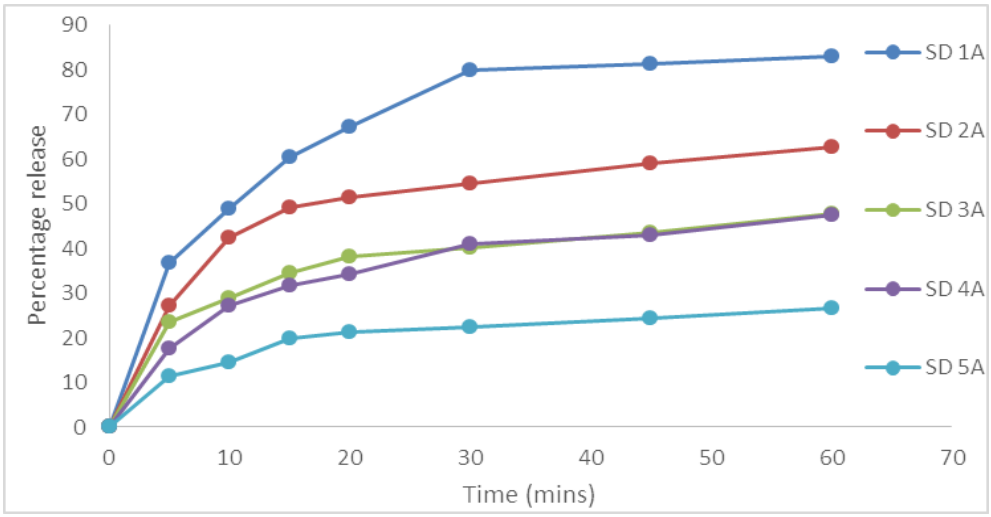

Fig 4: In vitro release studies of Formulations SD 1-A to SD 5-A [acid media]

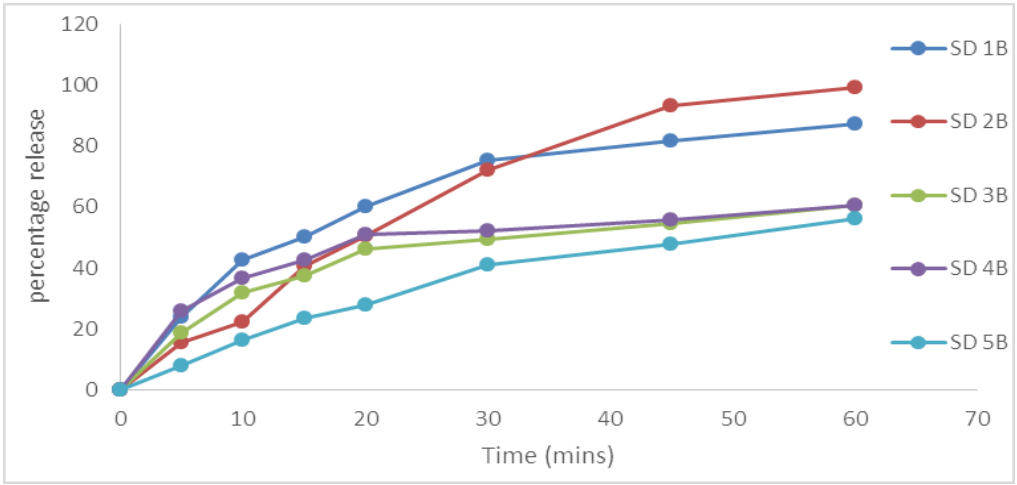

Fig 5: In vitro release studies of Formulations SD 1-B to SD 5-B [base media]

Table 6:Pre-compression parameters of formulations of FS 1 – FS 9.

Sl.no	Formulations	Bulk Density [gm/cc]	Tapped Density [gm/cc]	Compressibility Index [%]	Hausner's Ratio	Angle of repose [θ]
1	FS 1	0.384	0.414	7.24	1.07	24.33
2	FS 2	0.360	0.385	6.49	1.06	25.38
3	FS 3	0.385	0.420	8.33	1.09	26.82
4	FS 4	0.371	0.401	7.48	1.08	24.99
5	FS 5	0.363	0.406	10.59	1.11	26.71

6	FS 6	0.376	0.403	6.69	1.07	24.97
7	FS 7	0.362	0.387	7.52	1.05	25.48
8	FS 8	0.370	0.392	8.48	1.08	24.67
9	FS 9	0.382	0.410	9.63	1.06	25.89

Evaluation of Post-Compression Parameters of Verapamil Hcl

Table 7: Post-Compression Parameters of formulations FS-1 – FS-9

Sl.no	Tests	Specification	FS-1	FS-2	FS-3	FS-4	FS-5	FS-6	FS-7	FS-8	FS-9
1	Thickness [mm]	3.5-4.5	3.8	3.6	3.5	3.6	3.7	3.7	3.8	3.6	3.7
2	Hardness [kg/cm^2]	5.0-7.0	5.3	6.1	5.5	5.2	5.8	6.1	5.6	6.4	6.2
3	F*riability [%]*	Not more than 1%	0.14	0.11	0.15	0.12	0.17	0.16	0.12	0.16	0.13

Table 8: Weight variation and assay of formulations FS 1 - FS 9.

S.no	Formulation codes	Average weight [mg]	Weight variation [%]	Assay of Verapamil Hcl
1	FS 1	446±0.41	0.48	98±0.45
2	FS 2	450±0.29	0.16	99±0.62
3	FS 3	445±0.78	0.17	98±0.31
4	FS 4	448±0.12	0.16	99±0.79
5	FS 5	446±0.63	0.48	98±0.4
6	FS 6	448±0.33	0.53	99±0.68
7	FS 7	447±0.62	0.47	98±0.5
8	FS 8	451±0.29	0.16	100±0.6
9	FS 9	449±0.32	0.52	99±0.54

Table 9: In vitro release studies of Formulations FS 1 to FS 9

Time [Hours]	FS 1	FS 2	FS 3	FS 4	FS 5	FS 6	FS 7	FS 8	FS 9
0	0±0.00	0	0	0	0	0	0	0	0
1	16±0.2	15±0.92	6±0.36	12±0.03	15±0.92	10±0.47	13±0.04	12±0.02	14±0.08
2	21±0.25	21±0.01	10±0.94	17±0.85	21±0.01	18±0.74	16±0.35	22±0.15	19±0.10
3	36±0.22	32±0.99	20±0.5	35±0.42	32±0.99	36±0.66	30±0.48	28±0.12	30±0.18
4	44±0.59	40±0.87	25±0.15	43±0.71	40±0.87	46±0.93	42±0.56	37±0.16	39±0.28
5	52±0.72	47±0.24	30±0.46	52±0.91	47±0.24	52±0.5	48±0.85	45±0.36	48±0.46
6	58±0.39	55±0.19	34±0.57	65±0.06	55±0.19	58±0.91	56±0.89	56±0.56	59±0.72
7	68±0.31	63±0.29	38±0.94	75±0.15	63±0.29	65±0.91	62±0.58	60±0.66	68±0.77
8	76±0.49	70±0.84	42±0.51	80±0.47	70±0.84	71±0.2	72±0.42	68±0.78	76±0.65
9	83±0.93	78±0.54	48±0.52	85±0.06	78±0.54	76±0.91	77±0.55	84±0.82	86±0.91
10	84±0.19	82±0.61	53±0.25	89±0.09	82±0.61	84±0.53	84±0.68	87±0.92	89±0.86
11	89±0.18	89±0.5	59±0.17	91±0.06	89±0.5	88±0.28	86±0.48	90±0.88	94±0.90
12	93±0.76	96±0.62	70±0.56	95±0.43	96±0.62	97±0.24	94±0.36	95±0.66	96±0.64

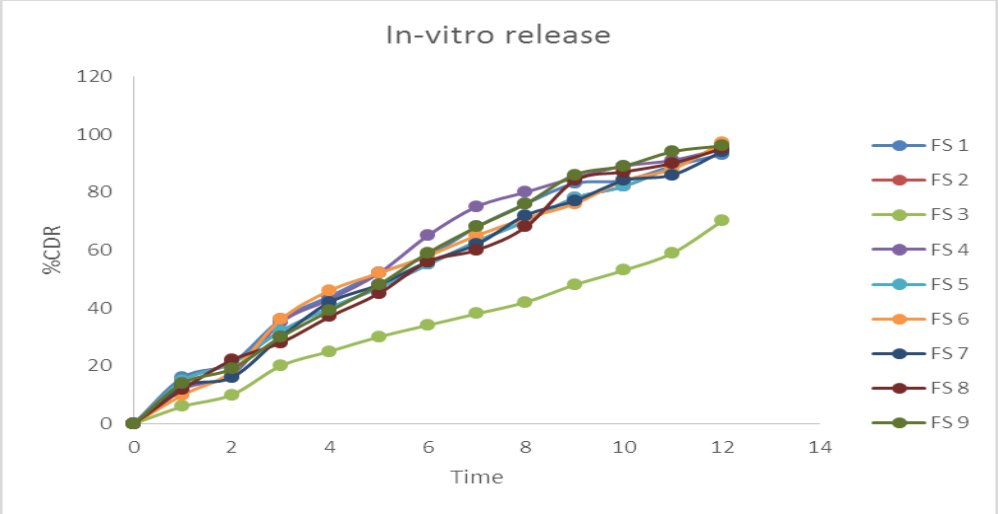

Fig6: In vitro graph of formulations FS 1 to FS 9

Table 10: Mathematical Model Fitting of Obtained Drug Release Data.

Formulation code	Zero order [R^2]	First order [R^2]	Higuchi Matrix diffusion [R^2]	Korsemeyerpeppa's	
				[R^2]	N
FS 1	0.9703	0.9681	0.9702	0.7337	1.229
FS 2	0.9912	0.8831	0.9608	0.7487	1.233
FS 3	0.9899	0.9472	0.922	0.8684	1.275
FS 4	0.9581	0.9724	0.9545	0.7899	1.3232
FS 5	0.9912	0.8831	0.9605	0.7487	1.2335
FS 6	0.9743	0.8596	0.9637	0.7489	1.3153
FS 7	0.9832	0.9317	0.9556	0.795	1.2839
FS 8	0.9887	0.9153	0.9427	0.7846	1.282
FS 9	0.9833	0.9326	0.9484	0.7776	1.2826

ZERO ORDER

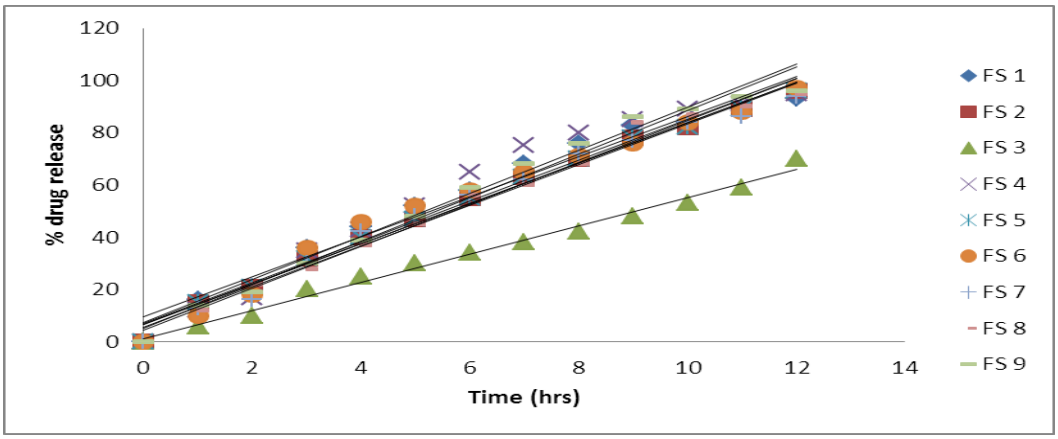

Fig 7: Zero order kinetics for SR

FIRST ORDER

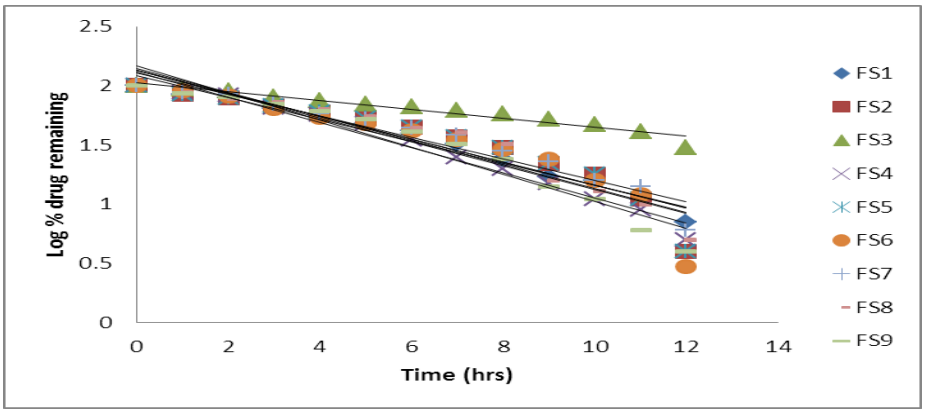

Fig 8: First order kinetics for SR

HIGUCHI MODEL

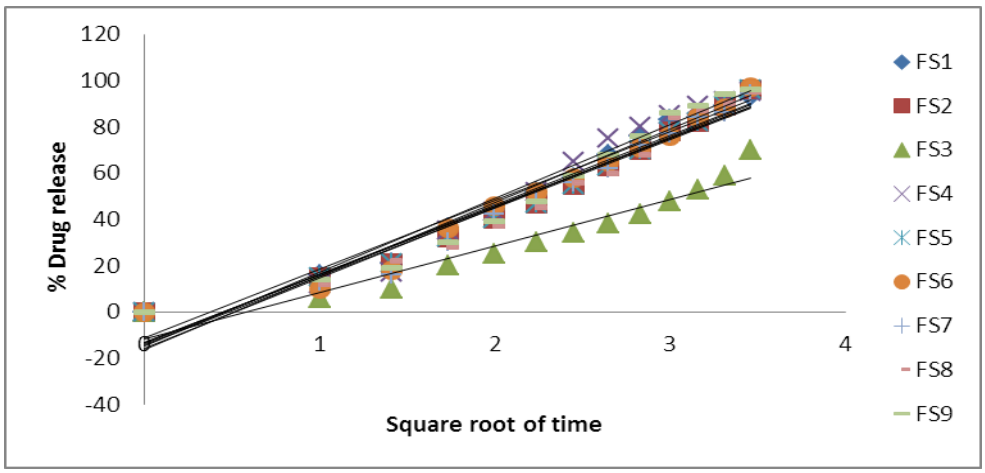

Fig 9: Higuchi release kinetics for SR

KORSEMEYER PEPPA'S

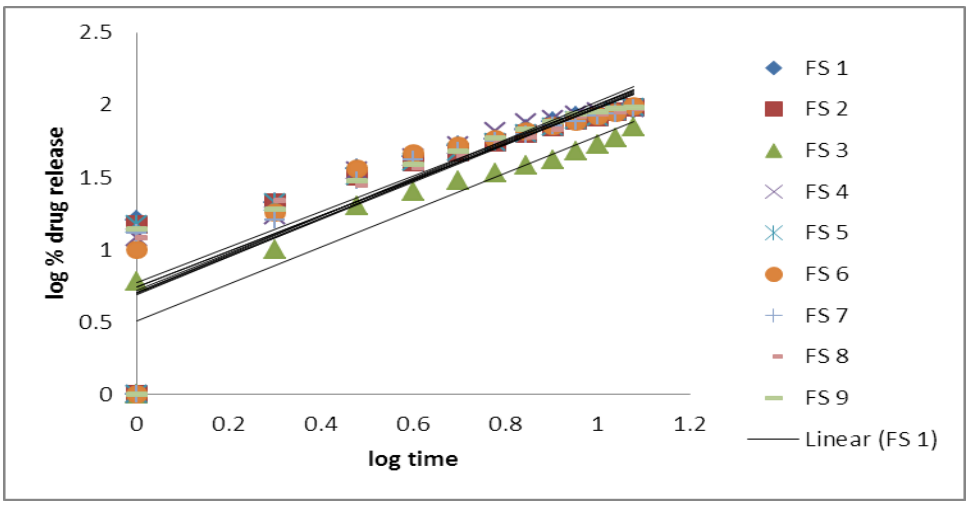

Fig 10: Korsemeyer-peppas release kinetics for SR

Stability studies of formulation [FS-6]

Table 11: Stability studies of formulation [FS-6] at 40°C/75%RH

S.no	Test	Formulation at 40^0C/75%RH			
		Initial	1-month	2-Months	3-Months
1	Hardness	6 kg/cm²	6 kg/cm²	5 kg/cm²	4 kg/cm²
2	Dissolution				
A	Time	2hrs in 1.2Ph HCl			
	1	12±0.03	12±0.01	11±.76	10.76
	2	17±0.85	17±0.42	16±.86	15.19
B		10hrs in 6.8Ph phosphate buffer			
	3	35±0.42	34±0.79	33±0.62	31±0.81
	4	43±0.71	42±0.14	41±0.89	40±0.99
	5	52±0.91	51±0.85	50±0.45	49±0.18
	6	65±0.06	64±0.87	64±0.91	63±0.63
	7	75±0.15	73±0.64	71±0.61	70±0.28
	8	80±0.47	79±0.61	78±0.45	76±0.85
	9	85±0.06	84±0.14	82±0.67	82±0.63
	10	89±0.09	87±0.89	86±0.12	84±0.86
	11	95±0.06	93±0.68	92±0.37	91±0.38
	12	97±0.43	96±0.66	94±0.17	93±0.81

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