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Formulation and Evaluation of Hydrogel Based Oral Controlled Drug Delivery System for Saquinavir

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Abstract

The main aim of this study was to develop hydrogel based controlled drug delivery system of Saquinavir mesylate as hard gelatin capsule which are able to deliver the drug at prolonged rate. The hydrogel was prepared by crosslinking HPMC 15 cps and Carbopol 971P and then granules are developed using MCC as diluent. Drug excipient compatibility was studied by FT-IR. The prepared hydrogels formulation are evaluated for Swelling index. Drug release from hydrogel was performed by using Franz diffusion cell. The prepared granules are evaluated for pre formulation studies (Bulk density, Tapped density, Angle of repose). The Saquinavir hydrogel capsule are evaluated for weight variation, Drug content uniformity (95%), Disintegration time (11 mins). In-vitro drug release studies are conducted for 12hrs by using USP type I apparatus which is showing drug release of 98%. From the drug release kinetics, it can be determined that the saquinavir hydrogel capsules drug release mechanism follows both the zero-order and Higuchi models. For all metrics, the formulation SHCF4 has demonstrated the best performance in accordance with pharmacopoeia standards.

Keywords: Hydrogel, controlled drug release, swelling index, Saquinavir mesylate.

1. INTRODUCTION

Hydrogels are defined as the three-dimensional networks of hydrophilic polymers which are held together by association bond and swell when they come in contact with water. These networks give physical integrity, mechanical strength, and occasionally take the form of a colloidal gel despite the fact that they are insoluble in water due to cross-linking caused by hydrogen bonds and ionic interactions [1]. The hydrogels have excellent swelling properties due to their strong thermodynamic affinity for solvent. Hydrogels have a high water content, which makes them biocompatible. The presence of various functional groups such as -COOH, $-NH_2$, -OH, $-CONH_2$, and $-SO_3H$ in hydrogels is what gives them their ability to hold water [2]. Hydrogels carry drug molecules to the gastro intestinal tract and improves absorption by prolonging the drug release. These drug delivery methods keep their integrity throughout the gastro intestinal tract and eventually swell in the gastro intestinal environment for a controlled drug release [3]. Hydrogels are prepared by ionizing radiation as it produces main-chain free radicals, which can then recombine to form cross-link junctions, Physical processes, such as electrostatics and chemical's reaction are also used for linking the polymer chains [4]. Ionic interactions, complicated coacervation, hydrogen bonding, freeze-thawing, and heating or cooling a polymer solution are a few examples of physical cross-linking techniques. Chemical cross-linking processes involve the inclusion of chemicals that promote cross-linking, such as epichlorohydrin, glutaraldehyde, etc [5]. These are divided into four types based of mechanism of action diffusion-controlled drug release, swelling controlled drug release, chemically controlled drug release, environment responsive systems [6].

A typical and practical way for taking the drugs into your systemic circulation is oral administration. The ease of administration, painlessness, accurate dosage, and affordable nature of oral administration make it a popular and practical approach for getting drugs into the systemic circulation. Conventional pharmaceuticals, however, must be administered in repeated dosages due to their low half-life and the need for long-term pharmacological therapy for chronic conditions, which leads to patient noncompliance and negative side effects. Designing

controlled release drug delivery methods could overcome this[7].

Controlled release drug delivery systems offer a consistent dose of the medication to the absorption site, facilitating the maintenance of plasma concentrations within the therapeutic range and minimizing adverse effects as well as administration frequency. Because they are flexible and allow for the establishment of a desired drug release profile, hydrophilic polymer matrix systems are frequently employed in oral controlled drug delivery systems [8]. For the formation of a hydrophilic matrix system, HPMC is the ideal option.

Saquinavir is an antiretroviral drug which is used to treat or prevent HIV/AIDS. The antiviral activity of Saquinavir causes inhibition of enzyme (protease) which critical for the HIV-1 viral lifecycle. Its structure is based on the "peptidomimetic" principle, in which the molecule has a hydroxy ethylene scaffold that resembles the typical peptide linkage (cleaved by HIV protease) but cannot be itself broken. Saquinavir causes the generation of immature, non-infectious viral particles by blocking HIV-1 protease activity and thereby the proteolysis of the Gag polyprotein. Controlling drug delivery was the main goal of the current study in order to increase saquinavir's oral absorption [9].

2. MATERIALS AND METHOD

Saquinavir mesylate obtained from Hetero Labs Limited, Hydroxy propyl methyl cellulose (HPMC 15cps) obtained from Research-Lab Fine Chem Industries, Xanthan gum obtained from Research-Lab Fine Chem Industries, Carbopol 971P NF polymer obtained from Lubrizol Advanced Materials Europe BVBA Chaussee de Wavre 1945, Micro crystalline cellulose (MCC) obtained from Accord Labs, Talc obtained from NR CHEM, Distilled water.

Preparation of HPMC and Carbopol gel:

Required quantities of HPMC and Carbopol are weighed and taken in the beaker then dissolved in 20ml of water. Then the solution is placed on the magnetic stirrer for 10mins and kept a side for 15mins. Different concentration are prepared 1:1(SHF1), 1:2(SHF2), 1:3(SHF3), 1:5(SHF4) respectively.

Preparation of HPMC and Xanthan gum gel:

Required quantities of HPMC and Xanthan gum are weighed and taken in the beaker then dissolved in 20ml of water. Then the solution is placed on the magnetic stirrer for 5mins. Different concentration are prepared 1:1(SHF5), 1:2(SHF6), 1:3(SHF7), 1:4(SHF8) respectively.

Preparation of Saquinavir Hydrogel granules:

The required amount of polymers were weighed (0.3g of HPC 15cps and 1.5g of Carbopol 971P) taken in beaker and dissolve in 20ml of water. Then the solution is placed on the magnetic stirrer for 15mins and it is kept a side for half an hour. The required quantity of saquinavir is added to the formed hydrogel and mixed (post loading of drug). The saquinavir hydrogel is taken in motor and to this required quantity of micro crystalline cellulose added. This mixture is made into a damp mass. The granules are prepared and kept for drying. Prepared granules are filled in the capsules.

Table-1: Formulation trials of Saquinavir hydrogel

Ingredients	SHF1	SHF2	SHF3	SHF4	SHF5	SHF6	SHF7	SHF8
Saquinavir	200mg	200mg	200mg	200mg	200mg	200mg	200mg	200mg
HPMC 15cps	0.3g	0.3g	0.3g	0.3g	-	-	-	-
Carbopol971P	0.3g	0.6g	0.9g	1.5g	-	-	-	-
Xanthan gum	-	-	-	-	0.1g	0.2g	0.2g	0.2g
HPMC 15cps	-	-	-	-	0.1g	0.4g	0.6g	0.8g
Propylene glycol	1ml	1ml	1ml	1ml	1ml	1ml	1ml	1ml
Water	20ml	20ml	20ml	20ml	20ml	20ml	20ml	20ml

3. METHODOLOGY:

3.1 UV SPECTRUM ANALYSIS:

Saquinavir drug sample was analyzed using UV spectroscopic methods in methanol to determine the maximum absorption.

The calibration curve of saquinavir was plotted by using methanol as a solvent.

10 mg of Saquinavir was weighed and diluted with methanol in 10ml volumetric flask to give a concentration of 1000 µg/ml. From this reserve solution,1ml was taken and diluted to 10ml to give a concentration of 100ppm. From this reserve solution, a range of concentrations of 2, 4, 6, 8, 10 µg/ml were prepared and the absorbance was measured between 200nm -700nm against a blank using UV-spectrophotometer.

3.2 FT-IR SPECTROPHOTOMETRY:

FTIR studies are performed to know the drug excipient compatibility. The samples were developed by thoroughly combining it with potassium bromide. Saquinavir pure IR spectrum and also with other excipients were obtained. The samples were scanned between 400 and 4000 cm-1.

4. EVALUATION:

4.1 Swelling index [8]:

Using pH 1.2(0.1HCL) pH 6.8 phosphate buffer, the swelling kinetics and equilibrium swelling ratio were calculated. Prior to soaking in the buffer solution at room temperature, the dried hydrogel discs were weighed. The discs were removed from the buffer solution after a certain amount of time, wiped with butter paper to remove any excess surface water, and weighed again. Analytical balancing measurements were made of the swell patches. until the weight of the patches stayed consistent, studies on swelling were performed.

4.2 Drug release studies for hydrogel:

To evaluate the drug release from hydrogel we use Franz diffusion cells, which have a 25 ml receptor compartment and a 1.8 cm2 effective diffusion area. A cellophane dialysis membrane with an 8000 Da molecular weight cut-off that had been hydrated with the receptor medium for 12 hours served as the connecting element between the donor and receptor compartments. A pH 7.4 phosphate buffer served as the releasing medium. Throughout the experiment, the receptor chamber's substance was continuously stirred with a magnetic stirrer. 37.5 °C +/- 0.5 °C were used for the experiment. The formulations were administered in finite doses to the donor compartment in almost equal weight units. At the various time intervals, an aliquot of 5 ml was removed and replaced with an equal volume of the release medium kept at the same temperature. The samples' drug content was assessed using a UV-Spectrophotometer.

4.3 Pre-formulation studies [10]:

4.3.1 Bulk density: It is the weight of powder or granules divided by its volume.

$$\text{Bulk density} = \frac{\text{weight of granules}}{\text{bulk volume}}$$

4.3.2 Tapped density: It is the weight of powder or granules divided by its tapped volume.

$$\text{Tapped density} = \frac{\text{weight of granules}}{\text{tapped volume}}$$

Bulk density (BD) and tapped density (TD) are determined by taking a suitable quantity of granules is weighed, added, and the initial volume was then noted in a 100 ml measuring cylinder. After then, the measuring cylinder was tapped at intervals of two seconds at a height of 2.5 cm until no additional changes in the volume.

4.3.3 Hausner's ratio: It is the ratio of tapped density to bulk density.

$$\text{Hausner's ratio} = \frac{\text{tapped density}}{\text{bulk density}}$$

Hausner's ratios that are less than 1.25 exhibit good flowing qualities more so than those that are greater. Moderate flowing characteristics can be seen in Hausner's ratios, which range from 1.25 to 1.6. More cohesive powders will be visible when Hausner's ratio is higher than 1.6.

4.3.4 Angle of repose: It is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is used to measure the flow of granules.

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

h = height of the pile.
r = radius of the surface.

If angle of repose valve is less than 20 then it shows excellent flow properties, if the value is in between 20-30 it is considered as good, if it is greater than 40 it means it has very poor flow properties.

4.3 Weight variation [11]:

This test is done by weighing 20 capsules individually, determining average weight per capsule and finding out weight variation of each capsule against the average value.

Table-2: Limits of weight variation

Weight	Allowed variation
Less than 300mg	10%
Equal or more than 300mg	7.5%

4.4 Disintegration test:

Disintegration of hard gelatin capsules is done to know whether the drug substance is fully available for dissolution and absorption from the gastrointestinal tract. six capsules are placed one in each tube and maintain the temperature of immersion fluid at 37±2℃ then the tubes are repeatedly lowered 30 times per minutes into the immersion fluid. If 1 or 2 capsules fail to disintegrate completely, take another 12 capsules and repeat the test. Of the total 18 capsules tested, at least 16 capsules should completely disintegrate.

Table-3: Disintegration time

Capsule type	Disintegration time
Hard gelatin capsule	30 mins
Soft gelatin capsule	60 ins

4.5 In – vitro dissolution studies [12]:

It is defined as the amount of drug substances that goes into solution per unit time under standardized conditions of liquid solid interface, temperature and solvent composition. In – vitro drug studies were carried out using USP dissolution apparatus type I at 50 rpm. The dissolution media consist of 900ml of 0.1N HCl (pH 1.2) for 2hours and then the media was changed to buffer solution (pH 6.8). The temperature of the dissolution media was maintained at 37±0.5℃. The dissolution is carried out for 12hours.The drug release at different time intervals was measured by ultraviolet visible spectrophotometer (Shimadzu). Different pharmacokinetic models can be used to analyse the drug release kinetics and explain in vitro drug release.

4.6. Drug Content uniformity:

It was performed by taking 10 capsules they were assayed individually by removing the contents from capsule and suitably diluted with methanol solution. Absorbance of the solution was measured by using UV spectrophotometer at 240nm by using methanol as blank. If 9 out 10 capsules fall within 85% - 115% and 10th capsule falls in the range of 75% - 125% then it was accepted. If more than 2 capsules deviate, then another 20 capsules were taken and assayed each capsule again. If 27 capsules are in the ±15% range and 3 capsules are in the ±25% then the capsules are accepted.

5. RESULTS AND DISCUSSION:

5.1 UV SPECTRUM ANALYSIS: Saquinavir drug sample was analyzed by UV spectrophotometer using methanol as solvent, the maximum absorption was found to be 240nm.

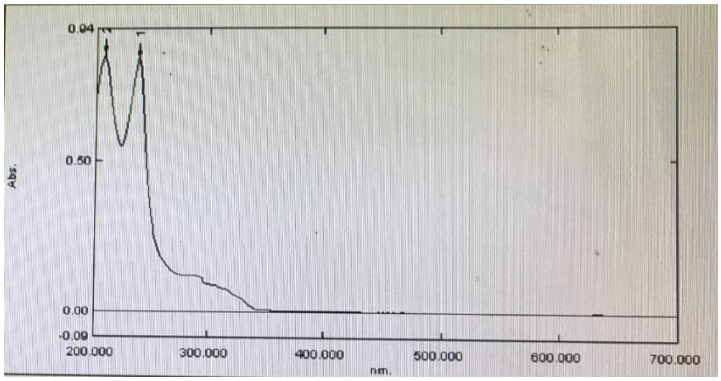

Fig-1: Absorbance maxima of Saquinavir.

UV Calibration of Saquinavir mesylate: The drug calibration curve follows Beer – Lambert's law. The absorbance is seen at 240nm.

Table-4: Absorbance of Saquinavir

Concentration	Absorbance at WL.240.
2PPM	0.071
4PPM	0.087
6PPM	0.101
8PPM	0.114
10PPM	0.131

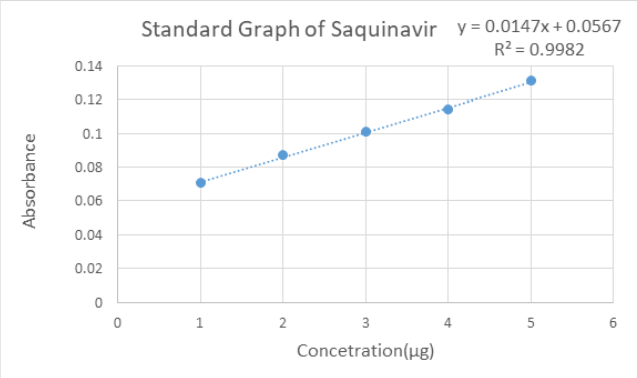

Fig-2: Standard Graph of Saquinavir

5.2 Selection of Hydrogel (Swelling index)

Table-5: Swelling index of Saquinavir hydrogel formulations

Time	SHF1	SHF2	SHF3	SHF4	SHF5	SHF6	SHF7	SHF8
15mins	20.25±0.4	28.2±0.15	34.14±0.3	40.64±0.12	38.81±0.11	40.52±0.23	43.1±0.35	45.69±0.52
30mins	35.18±0.34	39.43±0.2	56.24±0.21	55.94±0.44	50.69±0.34	52.07±0.45	53.15±0.24	51.08±0.17
45mins	58.01±0.21	60.15±0.23	77.12±0.5	73.65±0.32	78.1±0.53	67.17±0.19	60.24±0.39	63.32±0.44
1hr	65.14±0.6	67.08±0.42	86.13±0.35	83.78±0.14	81.67±0.28	76.35±0.53	75.12±0.18	87.16±0.35
2hr		73.55±0.65	91.05±0.41	94.10±0.51	92.05±0.43	92.07±0.37	87.3±0.25	100.75±0.51
4hr		86.11±0.26	99.45±0.19	111.03±0.13		115.8±0.41	92.01±0.39	111.81±0.4
6hr			105.56±0.22	119.12±0.6		128.78±0.18	109.67±0.51	125.1±0.3
8hr			120.7±0.47	128.54±0.49			123.7±0.54	131.07±0.49
10hr				135.78±0.25			138.4±0.16	140.1±0.34
12hr				147.34±0.16			151.71±0.28	152.12±0.26

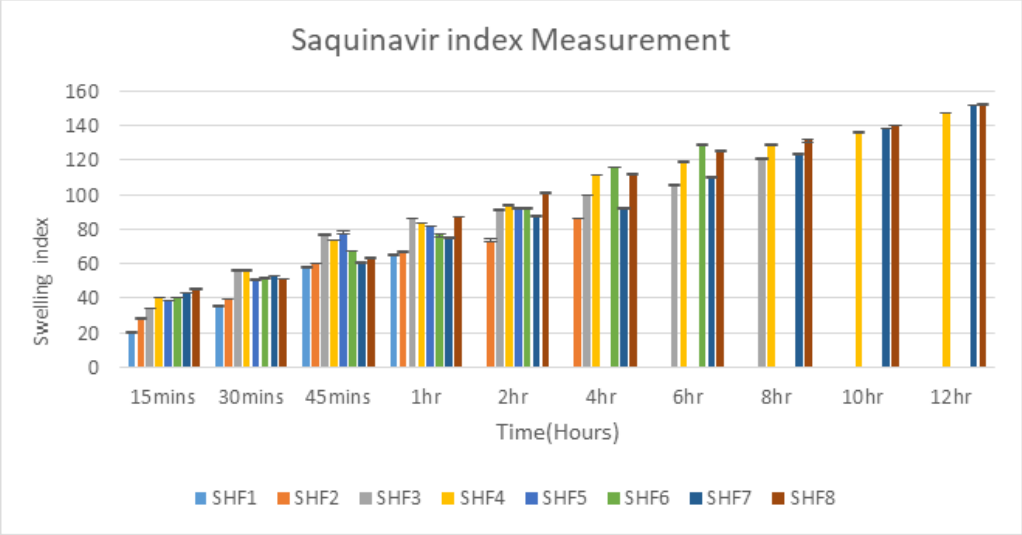

Fig-3: Graph of Swelling index of Saquinavir hydrogel formulation

By contrasting numerous elements, including consistency, swelling index, the aforementioned formulations are chosen (SHF4, SHF7). In order to find the optimal formulation, drug release experiments for the chosen hydrogels are carried out utilizing Franz diffusion cells.

5.3 Drug release studies from hydrogel:

Table-6: Drug release profile of optimized saquinavir hydrogel formulations selected from above table

Time	% Of cumulative drug release of SHF4	% Of cumulative drug release of SHF7
15mins	2.96	5.01
30mins	12.64	19.21
45mins	18.98	29.62
1hr	30.28	50.21
2hrs	37.01	78.28
4hrs	50.24	85.73
6hrs	72.14	98.78
8hrs	80.41	-
10hrs	87.11	-
12hrs	99.02	-

5.4 Preparation of Saquinavir hydrogel granules:

The results of the drug release trials demonstrate that SHF4 has a controlled drug release for 12 hours, whereas SHF7 has a controlled drug release for 6 hours. In view of the investigations, SHF4 is chosen as the optimal formulation for the following procedure. The hydrogel which was chosen formulated as granules by using different diluents.

Table-7: Formulation trials

Ingredients	SHCF1	SHCF2	SHCF3	SHCF4	SHCF5	SHCF6
Lactose anhydrate	590mg	-	-	-	-	-
Starch	-	450mg	-	-	-	-
Mannitol	-	-	450mg	-	-	-
MCC	-	-	-	270mg	-	-
Lactose monohydrate	-	-	-	-	1132mg	-
Dibasic calcium phosphate	-	-	-	-	-	450mg
Talc	5mg	5mg	5mg	5mg	5mg	5mg

According to the formation of granules and the amount of diluent utilized, SHCF2, SHCF3, SHCF4, and SHCF6 are considered the best formulations from the aforementioned table. A variety of pre formulation research are carried out for these chosen ones.

5.5 Pre-formulation studies of Saquinavir hydrogel granules:

Table-8: Pre formulation studies of SHCF2, SHCF3, SHCF4, SHCF6

Pre formulation studies	SHCF2	SHCF3	SHCF4	SHCF6
Tapped density	0.46±0.51	0.46±0.37	0.40±0.2	0.41±0.24
Bulk density	0.35±0.41	0.40±0.13	0.33±0.1	0.39±0.61
Hausner's ratio	1.31±0.3	1.15±0.22	1.21±0.16	1.78±0.52
Angle of repose	28.51±0.2	26.53±0.42	16.87±0.3	35.18±0.15

Based on the Angle of Repose and Hausner's ratio values, the optimal formulation from the previous investigations is SHCF2, SHCF3, and SHCF4. For these formulation weight variation and in vitro drug release studies are carried out.

5.6 Evaluation of Saquinavir hydrogel capsules

Table-9: Evaluation of Saquinavir hydrogel capsules

Formulations	Minimum weight(g)	Maximum weight(g)	Average weight(g) (mean ±SD)	Weight variation (%)	Disintegration time	Drug content uniformity
SHCF2	0.3474	0.3612	0.3453±0.0025	5.8	10mins	90%
SHCF3	0.3510	0.3812	0.3661±0.0018	4.1	11mins	87.5%
SHCF4	0.3412	0.3604	0.3449± 0.0025	2.03	10mins	95%

5.7 In vitro dissolution studies of Saquinavir hydrogel capsules

Table-10: In vitro drug release profile of SHCF2, SHCF3, SHCF4

Time	% Drug released of SHCF2	% Drug released of SHCF3	% Drug released of SHCF4
15mins	6.08±0.2	3.15±0.4	2.49±0.1
30mins	20.71±0.15	22.64±0.3	11.06±0.43
45mins	39.81±0.5	37.61±0.11	16.17±0.35
1hr	60.15±0.22	55.98±0.26	25.71±0.6
2hrs	76.75±0.6	73.17±0.35	36.30±0.33
4hrs	88.67±0.32	82.52±0.73	44.64±0.47
6hrs	98.14±0.25	97.13±0.69	62.64±0.28
8hrs	-	-	78.8±0.33
10hrs	-	-	89.64±0.4
12hrs	-	-	98.83±0.56

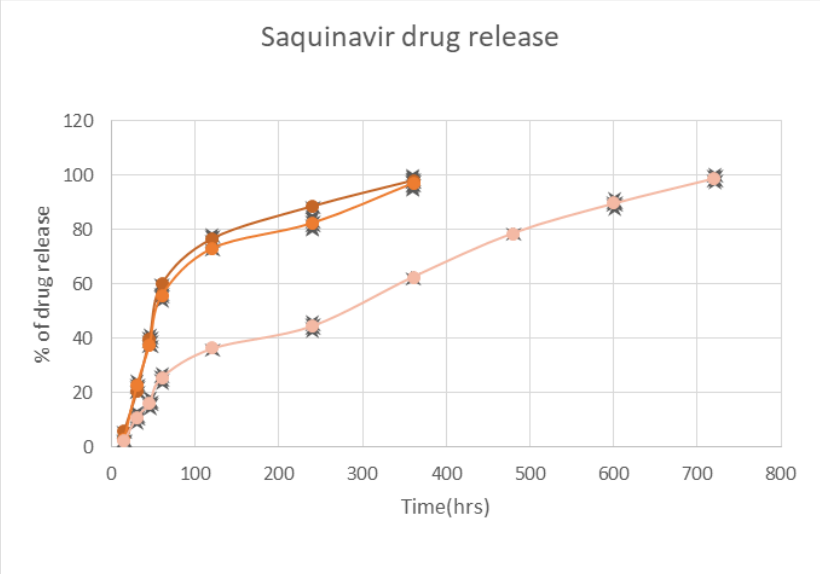

Fig-4: In vitro drug release profiles of SHCF2, SHCF3, SHCF4

From the results of in vitro drug release studies of formulations (SHCF2, SHCF3, SHCF4). SHCF4 is selected as optimized formulation as it is showing controlled drug release for 12hrs.

5.8 Drug Release kinetics: From results of drug release kinetics, it was determined that Saquinavir hydrogel capsules follow zero order and Higuchi model.

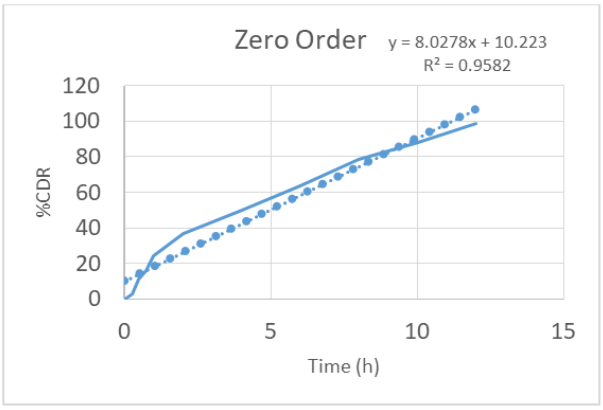

Fig-5: Zero-order kinetics

Fig-6: First order kinetics

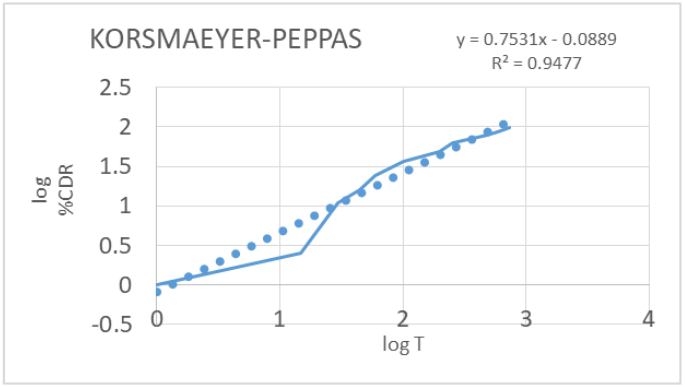

Fig-7: Higuchi model

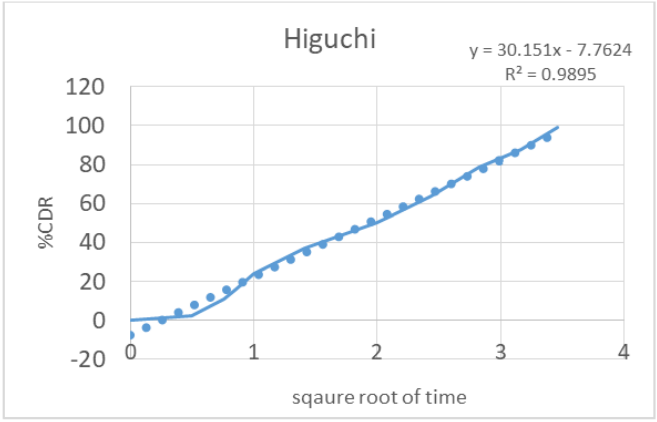

Fig-8: Korsmaeyer- peppas model

5.9 FT-IR Results:

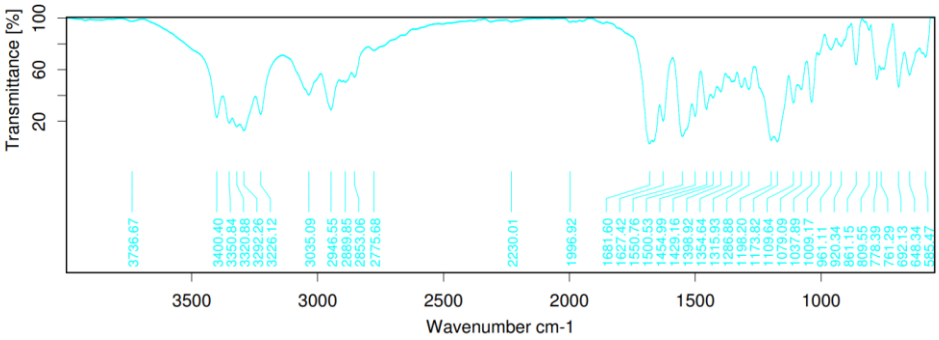

Fig-9: FT-IR of Saquinavir pure drug

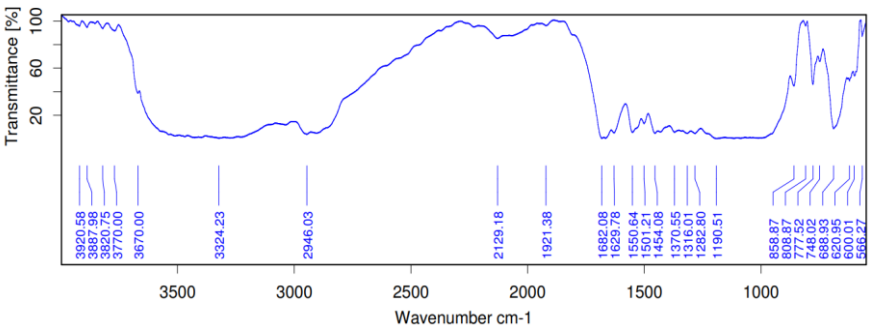

Fig 10: FT-IR of Saquinavir hydrogel formulation

Table-11: FT-IR of Saquinavir pure drug and Saquinavir formulation

S. No	Pure drug	Saquinavir formulations	Chemical bonds	Name
1	3736.67	3770.00	-OH Stretching	Alcohol
2	3400.00	3670.00	N-H Stretching	Primary amine
3	2946.55	2946.03	N-H Stretching	Amine salts
4	1996.92	1921.38	C=C=C	Alkene
5	1682.60	1682.07	C=O Stretching	Conjugated aldehyde
6	1627.42	1629.70	C=C Stretching	Alkene
7	1550.76	1550.64	N-O Stretching	Nitro compound
8	1454.99	1454.08	C-H bending	Alkene
9	1315.93	1316.01	O-H bending	Phenol
10	1286.88	1282.80	N-H	Aromatic amine

6. CONCLUSION

The FTIR analyses show that the drug was compatible with the polymers and other excipients utilized in the dosage form. All of the developed capsules were reported to fall within the defined range for weight uniformity, Disintegration time. All capsule formulations had the same amount of drug in them, which indicates that the drug was distributed evenly across the matrices. Based on in vitro drug release studies of SHCF2, SHCF3, SHCF4. Formulation SHCF4 was found to be showing prolonged drug release for 12hrs when compare to SHCF2, SHCF3. SHCF4 capsules are subjected to drug release kinetics. The formulation follow zero order kinetics and Higuchi model. Finally, it was determined that the Hydrogel-based Saquinavir capsules, formulation SHCF4 including HPMC 15 cps, Carbopol 971P(1:3), MCC exhibited swelling time and in-vitro drug release research slower than the other formulations.

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