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Original Research Article

FORMULATION AND IN VITRO EVALUATION OF IMMEDIATE RELEASE SOFTGEL OF NAPROXEN SODIUM

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Abstract: Oral drug delivery has been known for decades as the most widely utilized route of administered among all the routes that have been employed for the systemic delivery of drug via various pharmaceutical products of different dosage forms. The reasons that the oral route achieved such popularity may be in part attributed to its ease of administration and the belief that oral administration of the drug is well absorbed. One such area of research is design of Softgel technology. Softgel technology is one of the most attractive and promising approach for increasing oral bioavailability by means of increasing solubility of the poorly soluble drug. Naproxen Sodium is one of the most important Non-steroidal anti-inflammatory agents used in the treatment of acute to chronic pains, inflammation and it belongs to BCS class-II drug so as to increase its aqueous solubility for enhancing the bioavailability, it is formulated as a liquid filled soft gelatin capsules.

Key Words: Soft gel, Naproxen Sodium, bioavailability

Introduction: Soft gelatin capsules or soft gels are a single-unit solid dosage form, consisting of a liquid or semi-solid fill enveloped by a one-piece sealed elastic outer shell. The amount of drug or extract together with adjuvant is enclosed within a globular, oval or other shape of a soft shell. Soft gelatin capsules offer the possibility of delivering a liquid in a solid oral dosage form. The soft gel can contain the active ingredient in solution, suspension or emulsion which will inherently lead to better absorption of the active ingredient as compared with delivery in a tablet or as a powder[1,2,3].

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Advantages: Increased the Rate of Absorption of Drugs: This has been achieved by using a drug solution matrix in a soft gel formulation where by absorption is significantly faster than from other solid oral dosage forms, such as compressed tablets. While absorption of a poorly soluble drug from a tablet formulation is rate-limited by the need for disintegration into

granules before drug dissolution into gastrointestinal fluid, the solution-soft gel approach, the shell ruptures within minutes to release the drug solution, which leads to increase the rate of absorption of drugs[4,5].

Increased Bioavailability of Drugs: As well as increasing the rate of absorption, soft gel have also been reported to improve the extent of absorption, this can be particularly effective for hydrophobic drugs with a relatively high molecular weight.

Ex: protease inhibitor saquinavir as a soft gel formulation provided around three times the bioavailability of saquinavir as measured by the area under the plasma-time curve (AUC), compared to a hard-shell capsule formulation.

Decreased Variability of Plasmatic Drugs: High variability in drug plasma levels is a common characteristic of drugs with low bioavailability. By dosing drug optimally in solution, the plasma level variability of such drugs has been significantly reduced.

Ex: cyclic polypeptide drug cyclosporine was successfully improved by this approach by using a microemulsion preconcentration in a softgel[6,7,8].

Patient Compliance and Consumer Preference: A number of self-medicating consumer preference studies have been carried out in an attempt to gauge the relative perception of soft gels compared to hard shell capsules and tablets. By using a soft gel formulation it may be possible to reduce the dose administered in order to therapeutic effectiveness, in this way it is possible reduce the capsule size, which will further improve patient compliance.

Safety for Potent and Cytotoxic Drug: The mixing, granulation and compression/filling processes used in preparing tablets and hard shell capsules have been noted to generate a significant quantity of air-borne powders. By preparing a solution or suspension of drug, where the active component is essentially protected from the environment by the liquid, such safety concerns and associated toxicities have been significantly reduced.

Dose Uniformity of Low Dose Drugs: Content uniformity can be achieved for formulations containing drug doses in the microgram region. Improved homogeneity has been achieved by dissolving the drug in a liquid and then encapsulating the liquid matrix in a soft gel.

Product Stability: Liquid filled soft gel has beneficial to oxidative or hydrolytic degradable drugs. The liquid is prepared and encapsulated under a protective nitrogen atmosphere and the subsequently dried shell has very low oxygen permeability. The shell may be transparent and opaque. Opacity provides protection for photosensitive substances. Soft gel capsules are also protected against UV radiation and light, which provides stability to the supplement and minimizes the formation of free radicals, and prevents especially rancidity. Soft gelatin capsules offer many advantages in comparison with other delivery systems. They are easy to swallow, have no taste (unless gelatin is intentionally flavored) odors and provides an elegant look.[9.10,11]

Types of Liquid Fill Formulations Encapsulated:

- Hydrophilic vehicles (aqueous based fill formulation)
- Lipophilic vehicles (lipid based fill formulation)
- Self-emulsifying oils (oil + non-ionic surfactant)
- Self-emulsifying drug delivery system
- Self-microemulsifying drug delivery system
- Self-nanoemulsifying drug delivery system

a) Aqueous Based Fill Formulation (Hydrophilic Vehicles): Hydrophilic vehicles for soft gel fill formulations include polyethylene glycols (Ex: PEG 400, PEG 600), methoxy polyethylene glycols (Ex: MPEG 350, MPEG550), diethylene glycol monoethyl ether, tetrahydrofurfuryl alcohol polyethylene glycol, propylene carbonate, N-methyl-2-pyrrolidone(NMP), polyoxyethylene-poly-

oxypropylene copolymers, propylene glycol, water, glycerin and ethyl alcohol.

The use of propylene glycol, glycerin and water is restricted to less than 10% of the total fill formulation, as these vehicles can also act as plasticizers for the gelatin shell. Similarly, use of lower molecular weight polyethylene glycol (Ex: PEG 200, PEG in the fill formulation is limited due to their ability to diffuse into the shell and their by act as a gelatin plasticizers. The extent of diffusion of a polyethylene glycol from the fill into shell decreases with increase in its molecular weight[12,13,14].

Solubility Enhancers for Hydrophilic Vehicles

By using the solubility enhancers, can produce highly concentrated solutions for acidic, basic and amphoteric compounds in hydrophilic vehicles suitable for filling soft gels and also reduce the fill weight[15,16]. The improvement of solubility of some compounds in polyethylene glycol by 40-400% using an ionizing agent (i,e., counter-ion, neutralizing agent). For example , the solubility of acidic compounds like ibuprofen, naproxen, indomethacin, acetaminophen in polyethylene glycol can be enhanced through partial ionization of these compounds with a hydroxide ion species (Ex: sodium hydroxide, potassium hydroxide, ammonium hydroxide)[17,18]. When using these neutralization techniques to obtain a highly concentrated solution of a compound, it is essential to keep the apparent pH of the final fill formulation at least between 2.5 and 7.5. At pH values below 2.5 gelatin gets hydrolyzed causing leakage of the softgel, whereas at pH values above 7.5 gelatin may be either hydrolyzed or tanned (cross-linked) resulting in decreased solubility of the gelatin shell[19,20,21].

Aim and Objectives: The aim of the present study is to develop a pharmaceutically stable, enhance bio-availability and quality improved formulation of Naproxen sodium soft gelatin capsules. For achieve this goal various prototype formulation trials will be taken and evaluated. The formula will be finalized by comparing the *in vitro* dissolution profile with that of the marketed formulation.

Materials and Methodology: Gift sample of Naproxen sodium is received from M/s Merck Pharma ltd. Mumbai and the soft gelatin capsule shells are also received from the same factory .The remaining ingredients like propylene glycol, povidone, lactic acid etc are used from RIPS laboratory raw materials. Pre-formulation testing is an investigation of physical and chemical properties of a drug substance alone and combined with excipients. It is the first step in the rationale development of the dosage forms. Pre-formulation studies yield necessary knowledge to develop suitable formulations. It gives information about the nature of the drug substance. Hence, the following pre-formulation studies were performed for the obtained sample of drug.

- Organoleptic evaluation
- Particle size distribution
- Drug-excipient compatibility study
- Solubility Studies

UV method development for estimation of drug

The methods are described below,

Organoleptic Evaluation: The colour and odour of the Naproxen sodium were evaluated and tabulated using descriptive terminology.

Particle Size Determination: Dry Sieving Method: An accurately weighed quantity of test specimen was placed on the top (coarsest) sieve, and lid was replaced. The nest of sieves was agitated for 5 minutes. Then each sieve was carefully removed from the nest without loss of material. Each sieve was reweighed, and the weight of material on each sieve was determined. The weight of material in the collecting pan was also determined in a similar manner. The nest of sieves were reassembled and agitated for 5 minutes. Each sieve was removed and weighed the quantity. Upon completion of the analysis, the weights of material were reconciled. Total losses must not exceed 5% of the weight of the Original test specimen.

Determination of Melting Point: Capillary melting point or a melting–point apparatus are most often used for the determination of the melting point of a solid. A few crystals of the drug was placed in a thin walled capillary tube 10-15cm long about 1mm inside diameter and closed at end. The capillary, which contains the sample, and a thermometer were then suspended so they can be heated slowly and evenly. The temperature range at which the sample was melted was taken as the melting point.

Drug Excipient Compatibility Study

- **Physical Observation:** Physical mixtures of drug and excipients were prepared by grinding specific ratios of drug and excipients in a mortar. Sample of 3-4 grams was taken and loaded in a glass vial, covered with rubber stopper, sealed with aluminum cap and labeled properly. Samples were observed and colour was recorded for initial evaluation and loaded into stability chamber at temperature of 40^0c and 75% relative humidity, 25^0c and 60% relative humidity for 4 weeks Compatibility study. Samples were withdrawn at 1 week interval for four weeks and observed for any colour and odour change. At the end of 4^{th} week samples were removed, observations were recorded and further analysis was carried out using DSC and FTIR.

Table No 1: Drug-Excipient Compatibility Studies

SL. NO	Ingredients	Ratio	Qty of blend (gm)
1	API	1	1
2	API + purified water	1:0.23	1.353
3	API + PEG 400	1:3.18	4.598
4	API + PEG 600	1:3.18	4.598
5	API + Povidone K 12	1:0.23	1.353
6	API + Povidone K 30	1:0.23	1.353
7	API + Povidone K 17	1:0.23	1.353
8	API + Lactic acid	1:0.28	1.408
9	API + propylene glycol	1:0.23	1.353

Fourier Transform Infrared Spectroscopy (FT-IR)

Principle: FT-IR stands for Fourier Transform Infrared, the preferred method of infrared spectroscopy. In infrared spectroscopy, IR radiation is passed through a sample. Some of the infrared radiation is absorbed by the sample and some of it is passed transmitted. The resulting spectrum represents the molecular absorption and transmission, creating a Molecular finger prints of the sample. Like a finger print no two unique molecular structures produce the same infrared spectrum. This makes infrared spectroscopy useful for several types of analysis. FT-IR Samples were mixed with KBr in the ratio 1:100 and pressed into pellets. Pellets were analysed at wavelength range 4000-450cm^{-1} with resolution of as 4cm^{-1}.

Sample Preparation: Completely dried potassium bromide was transferred into a mortar. About 2 % of pure drug or with excipients was weighed in digital balance, mixed and grinded to a fine powder. Two stainless steel disks were taken out of the desiccators. A piece of the pre-cut cardboard (in the tin can next to the oven) on top of one disk was placed and cut out hole was filled with the finely ground mixture.

Analytical Methods

Preparation of Standard Stock: 100 mg of Naproxen sodium was taken and added to respective media in a 100 ml volumetric flask and volume was made up to 100 ml, resulting in a standard stock solution of 1000 mcg/ml.

Preparation of Working Stock: From the above prepared standard stock solution 10 ml was taken and added to respective buffer media in a 100 ml volumetric flask and volume was made up to 100 ml then obtained 100 mcg/ml

solutions. From the working stock solution dilutions were prepared using respective media.

Determination of Absorption Maxima: 10 µg/ml solutions were taken to determine absorption maxima. Initially blank buffer solution was kept and scanned in the region of 200-400 nm. Then sample was kept for analysis and scanned in the same region. Absorption maxima were found to be 272 nm. Hence all further analysis was carried out at 272 nm in 0.01N HCl (pH 2.01) ,0.1N HCl (pH 1.05) , pH 4.5 sodium acetate buffer, pH 7.5 phosphate buffer , pH 6.8 phosphate buffer.

Standard Curve of Drug in 0.1 N Hydrochloric Acid: 10mg of drug was accurately weighed and dissolved in 10ml methanol to prepare the stock solution. 10ml sample was taken from the above solution and diluted to 100 ml of 0.1N hydrochloric acid to prepare the working standard. The aliquot amount of this solution was diluted with 0.1N hydrochloric acid to get 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml; 50µg/ml of drug per ml of the final solution was obtained. Then the absorbance was measured in UV Spectrophotometer at 272 nm against 0.1N hydrochloric acid as blank and the regression equation was computed.

Standard Curve of Drug in pH 6.8 Phosphate Buffer: 10mg of drug was accurately weighed and dissolved in 10ml methanol to prepare the stock solution. 10ml sample was taken from the above solution and diluted to 100 ml of pH 6.8phosphate buffer to prepare the working standard. The aliquot amount of this solution was further diluted with pH 6.8 phosphate buffer to get 10µg/ml, 20µg/ml, 30µg/ml, 40µg/ml, 50µg/ml of drug per ml of the final solution. Then the absorbance was measured in UV Spectrophotometer at 272 nm against pH 6.8 phosphate buffer as blank and the regression equation was computed.

Formulation Development: Preparation of Soft Gelatin Capsules of Naproxen Sodium: Naproxen sodium soft gelatin capsules, each containing 220mg of Naproxen sodium were prepared by encapsulation of liquid fill medicament into a gelatin shell.

Step-1: Preparation of Medicament

- Collect calculated quantity of Polyethylene glycol and propylene glycol in medicament manufacturing tank by filter through #200 mesh nylon cloths.
- Add and dissolve Povidone K in the medicament manufacturing tank with continuous mixing and heated up to 70°C - 80°C. Add calculated quantity of Lactic acid and water into medicament manufacturing tank with continuous mixing.
- Add and dissolve calculated quantity of Naproxen sodium into the medicament manufacturing tank with continuous heating up to 85°C - 90°C and mixing for 90-120 minutes. Allow the medicament to cool to room temperature below 30°C. Unload the medicament into medicament holding tank by pass through #200 mesh nylon cloths.

Step-2: Preparation of Gelatin Mass

- Transfer the Glycerin & Sorbitol special solution, purified water by filter through #200 mesh nylon cloths under stirring into the Gelatin melter by applying vacuum and maintain the temperature 80°C - 85°C.
- Transfer the Gelatin into the Gelatin melter by applying vacuum with continuous mixing at fast speed and continuous heating for 90-120 minutes or till it gets completely melted. Maintain the gelatin mass temperature 60°C - 70°C.
- Carry out the de-aeration by applying vacuum at 600-650 mm of Hg for 30-45 minutes and remove the extra amount of water and air bubbles entrapped inside the Gelatin mass
- Check and ensure the gelatin mass should not contain gelatin lumps & air bubbles.
- Collect 15 mg of purified water in a SS vessel and dissolve FD&C Blue No.1, add into gelatin melter with continuous mixing.
- Rinse the SS vessel with 10mg of purified water and add into gelatin melter with continuous mixing for 20-30 minutes. Unload

the gelatin mass into pre heated gelatin holding tank temperature 55°C ± 5°C by pass through #40 mesh.

Table No: 2 Formulation Chart

Name of the Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)	F7 (mg)	F8 (mg)
Naproxen sodium	220	220	220	220	220	220	220	220
Polyethylene glycol-400	575	575	575	571	565	565	569	571
Propylene glycol	25	25	25	25	25	25	25	25
Povidone k-12			36		36			36
Povidone k-17		36					36	
Povidone k-30	36			36		36		
Lactic acid	44	44	44	48	54	54	50	50
Purified water	30	30	30	30	30	30	30	30
Total filled weight	**930**	**930**	**930**	**930**	**930**	**930**	**930**	**930**

Table No: 3 For the Preparation of Soft gelatine Capsule shells

Gelatin	264.10
Glycerin	23.17
Sorbitol special	101.92
FD&C Blue	0.27
Purified water	166.52
Weight of the shell	**556mg**

Figure No: 1 FTIR of Naproxen Sodium

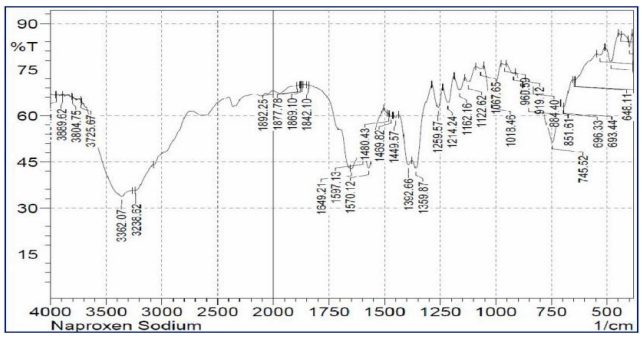
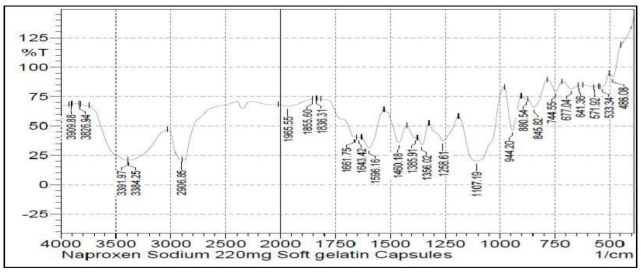


Figure No: 2 FTIR of Naproxen Sodium Soft Gelatin capsules



Calibration Curve of Naproxen Sodium in pH 7.4 Phosphate Buffer

Table No 4: Calibration Curve of Naproxen Sodium in pH 7.4 Phosphate Buffer

SL.NO	Concentration (µg/ml)	Absorbance
1	0	0
2	10	0.165
3	20	0.283
4	30	0.423
5	40	0.570
6	50	0.711

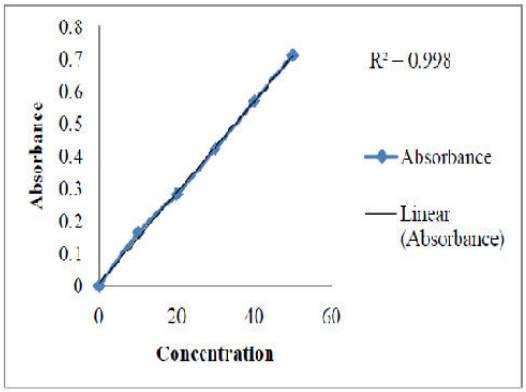


Figure No: 3 Calibration Curve of Drug in pH 6.8 Phosphate Buffer

Post Encapsulation Parameters:

Table No 5: Weight Variation, Hardness, and Disintegration Test of Dried Capsules

Formulation code	Weight variation			Hardness (N)	pH	Disintegration time (min)
	Gross weight (mg)	Fill weight (mg)	Shell weight(mg)			
F1	1443	887	556	7.8	7.2	13min
F2	1404.2	950.4	455.8	8.2	7.5	13min 27sec
F3	1374.2	916.7	457.5	8	7.6	12min 28sec
F4	1368.1	904.5	464.4	8.5	7.55	14 min
F5	1372	911.1	460.4	8.2	7.45	13min
F6	1375.4	914.6	460.8	8.2	7.4	14min
F7	1379.2	915.2	464	8.4	7.4	14min
F8	1375.4	921.4	454	8.5	7.42	13 min

Drug Content Estimation

Table No 6: Drug Content Estimation of Formulations Trails (F1-F8)

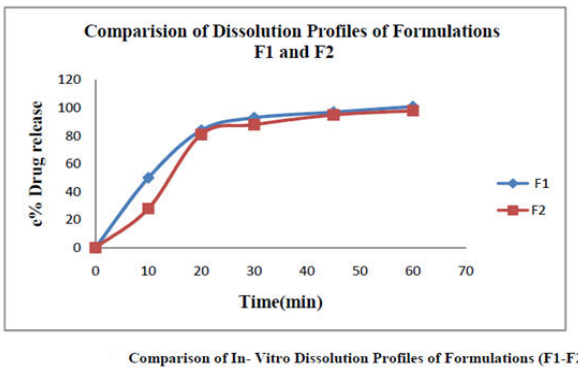
FORMULATIONS CODE	% DRUG CONTENT
F1	99.02
F2	100.12
F3	98.37
F4	99.21
F5	100.28
F6	99.37
F7	101.83
F8	99.75

In-vitro Drug Release Studies: The in-vitro dissolution studies were performed by using the USP-II (paddle) dissolution apparatus at 75 rpm. The dissolution medium consisted of 900ml of pH 7.4 phosphate buffer maintained at the temperature of 37±0.5 ^{o}c. An aliquot 10ml was withdrawn at specific time intervals and drug content was determined by UV-Visible spectrometer at 272nm.

In Vitro Dissolution Studies of Formulation Trails (F1-F8)

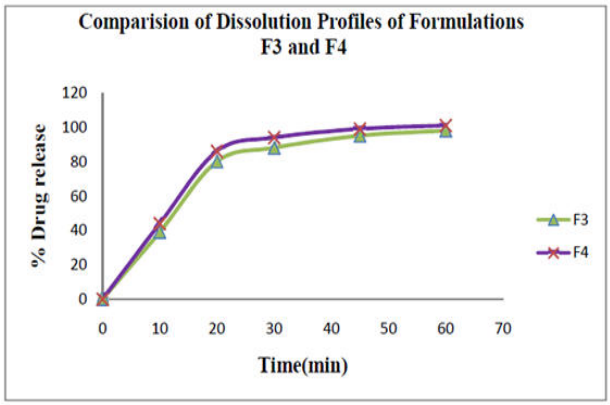
Table No 7: In Vitro Dissolution Studies of Formulations of (F1 – F8)

Time	F1	F2	F3	F4	F5	F6	F7	F8
0	0	0	0	0	0	0	0	0
10	50	28	39	44	51	53	51	35
20	84	81	80	86	81	74	85	61
30	93	88	88	94	89	84	89	79
45	97	95	95	99	97	90	92	93
60	101	98	98	101	98	96	98	98



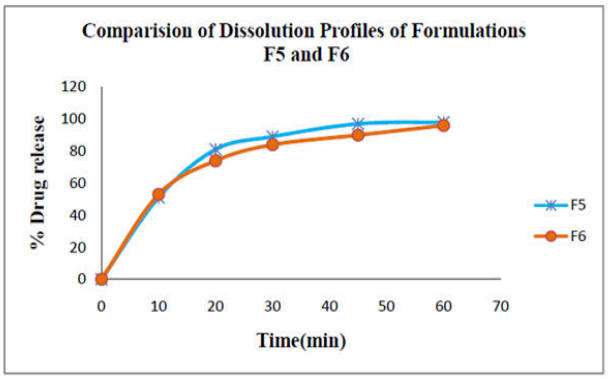
Comparison of In- Vitro Dissolution Profiles of Formulations (F1-F2)

Figure No: 4 Dissolution profiles of Formulation F1 & F2



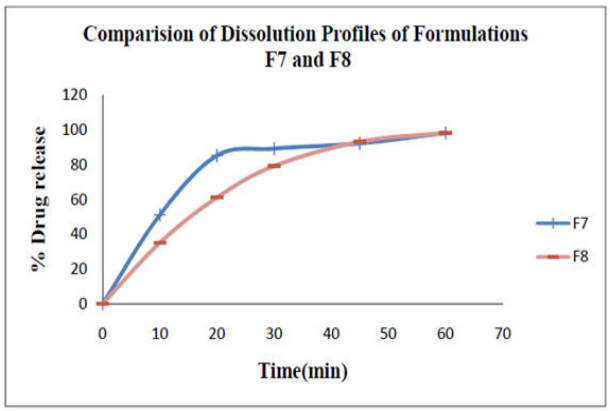
Comparison of In- Vitro Dissolution Profiles of Formulations (F3-F4)

Figure No: 5 Dissolution profiles of Formulation F3 & F4



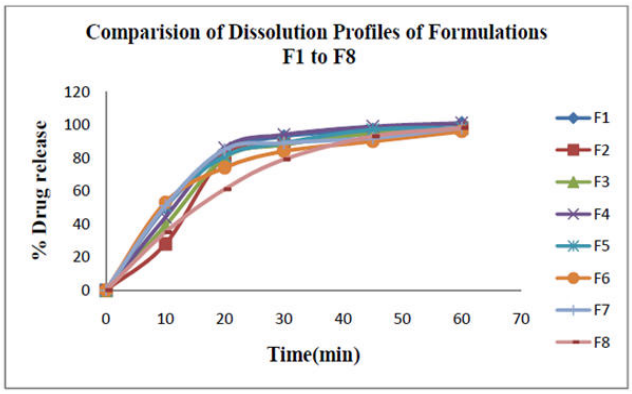
Comparison of In- Vitro Dissolution Profiles of Formulations (F5-F6)

Figure No: 6 Dissolution profiles of Formulation F5 & F6



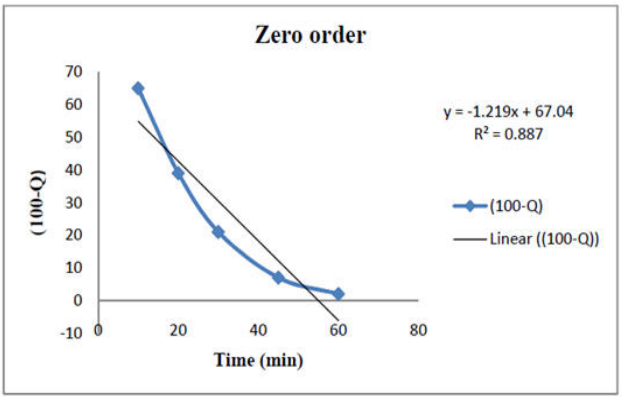
Comparison of In- Vitro Dissolution Profiles of Formulations (F7-F8)

Figure No: 7 Dissolution profiles of Formulation F7 & F8



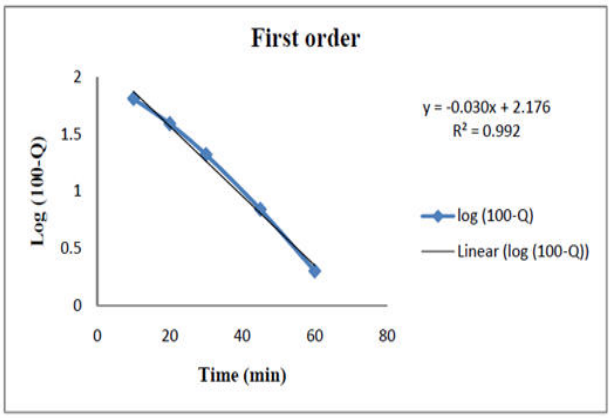
Comparison of In- Vitro Dissolution Profiles of Formulations (F1 to F8)

Figure No: 8 Comparison Dissolution profile of Formulation F1 to F8



Zero Order Kinetics Plot of Optimized Formulation (F8)

Figure No: 9 Zero Order Kinetics data



First Order Kinetics Plot of Optimized Formulation (F8)

Figure No: 10 First Order Kinetics data

Drug Release Kinetics for Optimized Formulation

Table No 8. Order of drug release kinetics for formulation F8

Order of kinetics	Zero order	First order
R^2Values	0.887	0.992

Conclusion: The basic goal of formulation is to achieve an enhanced bioavailability that is therapeutically effective and non-toxic, when compared to other oral solid dosage forms. The design of proper dosage form is an important element to accomplish this goal. One such area of research is design of Soft gel technology. Soft gel technology is one of the most attractive and promising approach for increasing oral bioavailability by means of increasing solubility of the poorly soluble drug. Naproxen Sodium is one of the most important Non-steroidal anti-inflammatory agents used in the treatment of acute to chronic pains, inflammation and it belongs to BCS class-II drug so as to increase its aqueous solubility for enhancing the bioavailability, it is formulated as a liquid filled soft gelatin capsules.. Preformulation study was performed by formulating binary mixtures of drug with selected excipients. Binary mixtures were screened for physical appearance at initial and 40°C 2°C / 75% ± 5% RH, 4 weeks in close condition. Physical observations of binary mixtures and FTIR study revealed that there is no incompatibility between Naproxen Sodium and selected excipients in the formulation, when exposed to accelerated stability condition of 40˚C/75%RH for 1 month. UV spectrophotometric analytical method was developed for the model drug in pH 7.4 Phosphate buffer. Absorption maxima were found to be at 272 nm and the linearity was fixed between the ranges of 10 to 50 µg/ml. various physical properties of like hardness, surface characteristics, practical size, pH weight variation and rupture time can significantly affect the rate of dissolution of drugs contained in a formulation. Various formulation trials of Naproxen Sodium Soft gelatin capsules were developed using various excipients for aqueous based fill formulation and gelatin shell formulation. Results of evaluation parameters like hardness, weight variation, pH of fill medicament, assay, disintegration test and encapsulation parameters were evaluated. Observations of all formulations for physical characterization had shown that, all of them comply with the specifications of official pharmacopoeias and/or standard references. The formulations was optimized for binder, re-crystallization inhibitor, solubilizer, pH modifier for fill formulation and plasticizer, different bloom strength of gelatine for gelatine shell formulation and evaluating different trials (F1-F8). Formulation F8 had showed better release profile. The in vitro drug release data obtained were extrapolated by zero order, First order to know the mechanism of drug release from the formulations. The release kinetics shows that the release of drug followed first order release in all the formulations. As the drug release was best fitted in First order kinetics, indicating that the rate of drug release is dependent on concentration. From the said observations it can be concluded that combination of lactic acid, povidone, propylene glycol, water, PEG 400, glycerin, sorbitol special and gelatin has shown effective release of Naproxen Sodium by increasing solubility and enhancing bioavailability. Hence it can be evident that by formulating the Naproxen Sodium soft gelatin capsules by soft gel technology which results in more effective release of drug, increased solubility and oral bioavailability may also be enhanced.

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