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FORMULATION AND EVALUATION OF SOFTGEL FOR DELIVERY OF COMPOUNDS WITH POOR ORAL BIOAVAILABILITY

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ABSTRACT

The aim of this research was to prepare a pharmaceutical composition containing nonsteroidal anti-inflammatory agent.

The present invention provides, stable and clear solution of Ibuprofen Sodium Dihydrate in soft gelatin capsules, which when taken orally release the contents of capsule into media of gastrointestinal tract. Since the model drug is water soluble, it does not precipitate in the contents of GIT.

The effects of various solubilizing agents, Co-solubilizing agents, Solubility enhancer were studied. Developmental trials were conducted for deriving a quantitative formula. The optimized drug fill formulations were formulated by using combinations of Oleic acid, Water, Sodium Lauryl Sulphate and Propylene Glycol. Trials were also done on optimizing the Gelatin paste for encapsulation.

The Assay, Identification and Dissolution profiles were done mainly by a precise and accurate HPLC method. Compatibility studies such as FTIR, Differential Scanning Calorimetry (DSC) studies revealed that the Drug and Excipients used were compatible. Thus a successful stable formulation of soft gelatin capsules of Ibuprofen Sodium Dihydrate (ISD) having adequate therapeutic efficacy was formulated.

KEYWORDS : *NSAIDS, Ibuprofen Sodium Dihydrate (ISD), Softgel, FTIR, HPLC, DSC.*

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INTRODUCTION

The soft gelatin capsule dosage form has been around for many years. The earliest soft gels date back to the 19th century, since then, many improvements have been made with respect to the production of these soft gel capsules.

The soft gelatin capsule 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 powder. Soft gelatin capsules are therefore the ideal solution and some times the only solution for delivery of compounds with poor oral bioavailability. Other properties that make soft gelatin capsule a useful and frequently applied dosage form include their aesthetic properties & 'Swallow ability', their tamper resistance, their protection of the active ingredient from light and oxidation, their taste-masking of ingredients & their masking of unpleasant odors of ingredients.

Advantages 1. Soft gel Reformulation for Life-cycle Management.

Softgels have ability to enhance bioavailability not only makes them the preferred dosage form for new chemical entities with poor oral bioavailability, they can also be used for reformulation of existing drugs, with the purpose of life-cycle extension. Two of such applications are described here.

2. Life -cycle lengthening through new therapeutic indications.

Compounds that are currently being delivered in a tablet or a capsule could be reformulated in a softgel so as to improve their bioavailability. The compound would then exert the same therapeutic effect at a lower dose level. As a result, the reformulated drug can be promoted

- With a new branded-name;
- For a new indication;
- In a new , more appealing dosage form; and
- At a dose level that is not easily copied by generic versions of the original dosage form.

3. Life -cycle Lengthening through Product Enhancement – Faster onset of action.

OBJECTIVE:

The potential drug candidate selected for this is Ibuprofen Sodium Dihydrate. Ibuprofen is insoluble in water though it has 95% oral absorption and it has been converted into salt form Ibuprofen Sodium Dihydrate to further enhance the bioavailability.

- To develop a soft gelatin capsule formulations of ISD which have increased therapeutic efficacy and aimed at achieving commercial viability.
- To study the effect of various variants on enhancing therapeutic efficacy and a dosage form which has optimum shelf life under ideal conditions.
- To prepare cost effective dosage form having patient compliance.

Hence, Research directions have been channelized to develop formulations of Soft Gelatin Capsule which have patient compliance and also efforts have been made to develop cost effective dosage form.

MATERIALS AND METHODS:

Experimental work involves

Preformulation study: Preformulation studies were carried out on drug.

Formulation Development: Developmental trials were conducted with excipients as shown in Table 1 for deriving a quantitative formula.

Table 1: Solubility trials for fill optimization

Ingredients	Qty. in mg									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
ISD*	257	257	257	257	257	257	257	257	257	257
Glycerin	-	-	-	-	35	-	-	40	35	35
PEG-400	400	450	100	150	100	-	-	-	-	-
PEG-600	-	-	300	223	238	400	386	373	473	373
Propylene glycol	43	47	47	-	-	46	67	35	35	35
SLS	-	6	6	-	-	-	-	-	-	-
Labrasol	-	-	-	70	70	-	-	-	-	-
Fill weight	**700**	**760**	**710**	**700**	**700**	**703**	**710**	**705**	**800**	**700**

Ingredients	Qty. in mg									
	F11	F12	F13	F14	F15	F16	F17	F18	F19	F20
ISD*	257	257	257	257	257	257	257	257	257	257
Glycerin	35	35	-	-	-	-	-	-	-	-
Maisine-35	-	-	-	-	195	-	-	195	195	-
PEG-600	338	352	-	-	-	-	-	-	-	-
PVP K 30	-	21	-	-	-	-	-	-	-	-
Propylene glycol	35	35		-	57		-	57	57	20
SLS	-	-	-	-	-	-	-	-	-	13
Transcutol	-	-	-	-	57	50	-	57	-	-
Labrasol	35	-	-	-	-	-	-	-	-	-
Tween-80	-	-	93	93	-	-	-	-	-	-
Labrafac	-	-	75	75	-	-	-	-	-	-
Oleic acid	-	-	-	-	-	343	408		-	410
Purified water	-	-	-	-	-	-	35	-	-	-
Cremophor ES 35	-	-	-	-	-	50	-	-	-	-
Cremophor RH 40	-	-	-	-	234	-	-	234	230	-
Capmul-PG-8	-	-	182	182	-	-	-	-	-	-
Capmul-MCM-8	-	-	93	93	-	-	-	-	-	-
Ethanol	-	-	-	-	-	-	-	-	61	-
Fill weight	**700**	**700**	**700**	**700**	**800**	**700**	**700**	**800**	**800**	**700**

*Ibuprofen Sodium Dihydrate

Method for drug fill preparation:

In the present research work total 20 fill solubility trials were carried out. The concentration of drug kept constant (257mg) across F1 to F20 trials. The concentration of solubilizer and co-solubilizer were varied as tabulated in Table 1 and stirred on magnetic stirrer to get a clear solution. Heating may be applied in few formulations between 50ºC to 70ºC to get a stable clear solution.

Gelatin paste preparation:

Charged the plasticizer, purified water, glycin and citric acid into a melter and heated to 80°C to 85°C. Gelatin powder was added to above solution and mixed well to get a gel free from lumps and air bubbles. Vacuum was applied for removing air bubbles and lumps.

Encapsulation:

The gelatin mass was fed by gravity to a metering device (spreader box) of encapsulation machine, which controls the flow of the mass onto air-cooled (13ºC to14ºC) rotating drums. Gelatin ribbons of controlled (±10%) thickness are formed. The wet shell thickness may vary from 0.022 to 0.045 inch. The ribbons are fed through a mineral oil lubricating bath, over guide rolls and then down between the wedge and the die rolls. Encapsulation machine was set with all standard change parts with oblong die rolls as shown in Table 2.

Table 2: Encapsulation machine parameters

Parameters	Batch F18	Batch F20
Gelatin tank temperature	60°C	60°C
Spreader box temperature	Left:55°C Right: 55°C	Left:55°C Right: 55°C
Cooling drum temperature	14°C	14°C
Segment temperature	4°C	4°C
Ribbon thickness	Left: 34 Right: 34	Left: 34 Right: 34
Machine RPM	2.25	2.25
Target fill weight	700mg	700mg
Area/room temperature	24°C and 30%RH	24°C and 30%RH

Tumble drying: After encapsulation, the capsules were very soft and sticky, due to the high moisture content and the remaining thin film of mineral oil. The capsule tumble dryer was used to remove the mineral oil and to accelerate the drying process.

Tunnel dryer:

The capsules were moved into drying rooms where dry air is circulated around them for a period of up to 48 hours.

Sizing:

To ensure that the capsules contain the proper dosage, an automatic "capsule sizing machine" is used to eliminate undersized and oversized capsules.

Inspection:

Capsules were submitted to a final quality check before packaging including visual inspection to check for malformed, damaged or improperly filled capsules. They were then packed.

Evaluation of Soft Gelatin Capsules

Identification:

In the test for assay, check whether the retention time of the major peak for ISD in the chromatogram of the sample solution corresponded to that in the chromatogram of the standard solution, as obtained in the Assay.

Average weight:

Weigh 20 capsules and note down the weight in gram. The average weight of capsule calculated by using the following formula:

$$\text{Average weight of capsules (gm)} = \frac{\text{Weight of 20 capsules (gm)}}{20}$$

Average fill weight of capsule:

Take gross weight of 20 capsules in gram from average weight test and weight of 20 empty shells in gram from the Uniformity of fill weight test. The average weight (fill) was calculated using the following expression:

$$\text{Average weight of capsules (gm)} = \frac{\text{Gross weight of capsules (gm)} - \text{Weight of 20 empty shells (gm)}}{20}$$

Uniformity of fill weight:

Weigh the intact capsules, taken for average weight of capsules individually and record the individual gross weight in 'gram' up to fourth decimal. Care was taken to preserve the identity of each capsule. Removed the content (fill) of all the 20 capsules individually by cutting one side of the shell and then wash repeatedly with petroleum ether LR grade (40ºC -60ºC) to remove the traces of medicament and then wipe the shells with tissue paper. Weigh and subtract the weight of empty shell of all the 20 capsules individually from the respective gross weight of the same capsule. This value gives the net content of individual capsule. The uniformity of weight was calculated using the expression:

$$\left[\frac{\text{Lower fill weight of the capsule in gram}}{\text{Average fill weight of the capsule in gram}} \times 100\right] - 100 = \%$$

$$\left[\frac{\text{Highest fill weight of the capsule in gram}}{\text{Average fill weight of the capsule in gram}} \times 100\right] - 100 = \%$$

Disintegration time:

Instrument: Disintegration Test Apparatus **Make:** Electrolab ED-2L

Procedure: Introduced six capsules into the basket rack assembly of disintegration test apparatus and add discs to each tube. Ensured that the temperature of bath liquid and water are 37ºC±2ºC. Immerse the assembly in water and start the apparatus. Record the time in minutes at which last, of the six, capsules disintegrate completely except fragments from the capsule shell.

Capsule size:

Instrument: Vernier calipers Digital **Make:** Mitasyo

Procedure: The length and breadth of 10 capsules were measured by using Vernier calipers and calculated the mean in millimeter (mm) and range.

Hardness:

Instrument: Softgel Hardness tester **Make:** Barreiss Hardness Tester

Procedure: Capsule is compressed to a certain extent between a measuring detector and a slowly moving plate. The counter force exerted by the capsules is displayed in Newton (N). The hardness was checked by keeping the capsule horizontally. Checked the hardness in Newton (N) of 10 capsules randomly selected.

Dissolution:

Instrument: Dissolution test apparatus **Make:** Electrolab TDT-08L

Preparation of standard solution: Weigh accurately about 22.0 mg of Ibuprofen sodium Dihydrate standard and transfer into 100 ml volumetric flask. Dissolved in sufficient volume of dissolution medium and diluted up to mark with dissolution medium and the dissolution medium was used as blank.

The operating conditions

Apparatus: USP-II (paddle), Media volume: 900ml (Dissolution medium), RPM: 50, Time point: 45 minutes and Temperature: 37ºC± 0.5ºC.

Preparation of sample solution: Switch on the dissolution test apparatus and fill the washed bowls with 900 ml each of dissolution medium. Allow the bath liquid and medium to attain the temperature of 37ºC± 0.5ºC. Placed six capsules separately in six bowls and started the instrument. After the specified time withdraw required of the specimen from a zone midway between the surface of the dissolution medium and the top of the rotating paddle not less than 1 cm from the vessel wall. Filtered the sample through whatman No.42 filter paper. Discard the first few ml of the filtrate. Collect the filtrate in six separate test tubes respectively.

HPLC analytical method: The conditions were as follows

Column: Cosmosil C18, 250 mm X 4.6 mm, 5µm, Detection: 264 nm, Flow rate: 1.5 ml/minute, Injection volume: 20µl, Temperature: 25ºC and Retention time of main peak: 7.5 minutes.

Procedure: Filter the blank, standard solution and sample solution through 0.45µ filter. Separately inject blank in single and standard solution (5 injections) and record the chromatogram. % Relative standard deviation: Not more than 2.0% for 5 replicate injections for each peak. If the system suitability parameters are within limit and then inject sample solutions (1 injection) and record the chromatogram. Calculate the % Ibuprofen Sodium Dihydrate released using the following formula:

$$= \frac{AT}{AS} \times \frac{WS}{DS} \times \frac{DT}{I} \times \frac{P}{100} \times \frac{100}{LC}$$

AT: Area of ISD peaks from sample solution chromatogram.

AS: Average area of Ibuprofen sodium Dihydrate peaks from standard solution chromatogram.

WS: Weight of ISD standard taken in mg.

DS: Dilution of standard solution.

DT: Dilution of sample solution.

P: Purity of ISD standard in % w/w on as is basis.

LC: Label claim of Ibuprofen sodium Dihydrate as mg per capsule.

Uniformity of dosage units (by weight variation):

From the fill weight of individual capsules performed in average fill weight test and from the result of the assay, calculate the content for 10 capsules as follow:

$$\text{Content of Ibuprofen Sodium Dihydrate in \%} = \frac{\text{Fill weight of a capsule (mg)}}{\text{Average fill weight of capsule (mg)}} \times \text{Assay (\%)}$$

Compatibility Studies:

The formulation of a dosage form requires consideration of the physical, chemical and biological characteristics of the drug and excipients used in fabricating the product. The drug and excipients must be compatible with one another to produce a product that is stable, efficacious, attractive, easy to administer and safe. The FTIR and DSC were done to establish that the active drug has not undergone any changes, after it has been subjected to processing steps during formulation of Softgels.

Stability studies:

Stability studies were carried out at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH as per ICH guidelines.

Packaging studies:

The different types of formulation were placed in blister packs to protect the formulation from moisture in the environment. Polyvinyl Chloride (PVC) and High Density Polyethylene (HDPE) were used for the more challenging environment. The packaging materials used to form blister were designed to minimize the rate of moisture uptake to an extent, which gives maximum shelf-life stability.

RESULTS:

Preformulation studies were carried out on drug. All the parameters are mentioned in Table 3 and Table 4. Standard curve of drug is given in graph 1.

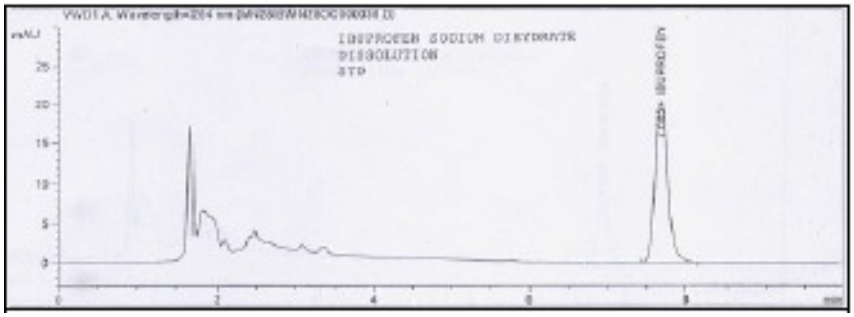
Table 3: Preformulation studies of drug

Parameters	Observation
Description	White powder
Solubility	Complies
Identification	Complies
Appearance of the solution (10%w/v)	Clear and colorless solution.
Assay	99.60%
Related Substances	Not Reported
Individual Impurities	
Total impurities	
pH	7.8
Specific rotation	0.00º
Loss on drying	14.60%

Table 4: Bulk density and Tapped density of drug

Test	Result
Bulk density	0.385g/mL
Tapped density	0.516g/mL
Carr's Index	25.4

Graph 1: HPLC Standard curve of Ibuprofen Sodium Dihydrate



Formulation development:

Formulation Solubility studies data are given in the table and it was noted that except F18 and F20, all other formulations precipitated and solidified. Evaluation parameters results are shown in the Table 5.

Table 5: Evaluation Tests For F18 And F20

Evaluation parameters	F18	F20
Average weight	1.0328gm	1.0772gm
Avg. fill weight of capsule	0.697gm	0.705gm
Uniformity of fill weight	-4.3% , +1.00%	-1.41% , +2.12%
Disintegration time	12. 04sec	11.89sec
Avg. Capsule size	21.39mm	21.39mm
Avg. Hardness	5.92N	5.46N

Microbial limits	Passes	Passes
Related substances	Complies	Complies
Assay	97.50%	101.50%

Table 6: Trials For Shell Composition

Ingredients	Shell formula (Qty Kg/Batch)		
	G1	G2	G3
Gelatin-A	12.500	12.500	12.500
Sorbitol Special	2.500	3.000	2.500
Glycerin	2.500	2.000	2.000
Glycin	0.625	0.600	0.550
Citric acid anhydrous	0.125	0.125	0.125
FD & C Blue-1	0.230	0.230	0.230
D&C Yellow 10	0.200	0.200	0.200
Purified Water	7.000	7.000	7.000

Dissolution profile of F18 and F20 are given Table 7.

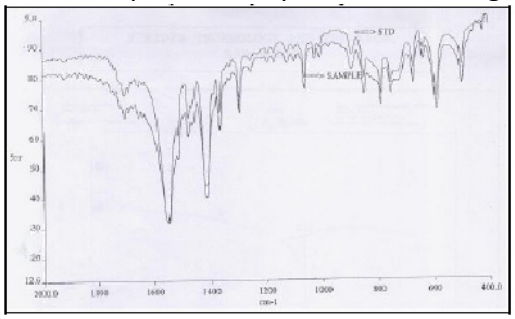
Table 7: Dissolution Profile Of F18 and F20

Trial No.	Time	Spl.Area	Corr. Factor	Minimum % release	Maximum % release	Average % release
F18	60 min	195.94637 208.34857	0.96543 1.02653	76.6	96.10	89.06
F20	60 min	218.39816 223.35278	1.10881 1.13397	99.3	101.2	100.25

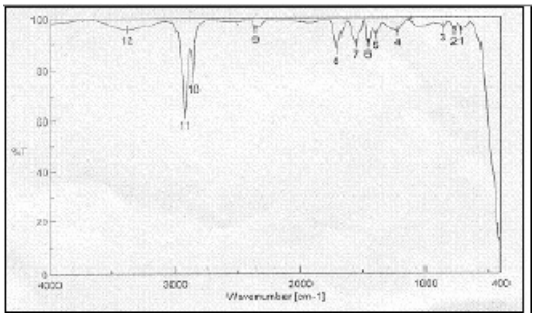
Compatibility study: The FTIR & DSC results were as shown in the graphs below.

FTIR: The FTIR spectrums are mentioned in Graph 2, Graph 3, Graph 4 and Graph 5.

Graph 2: FTIR Spectrum of Drug

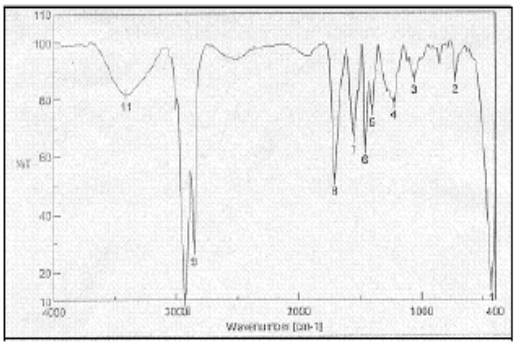


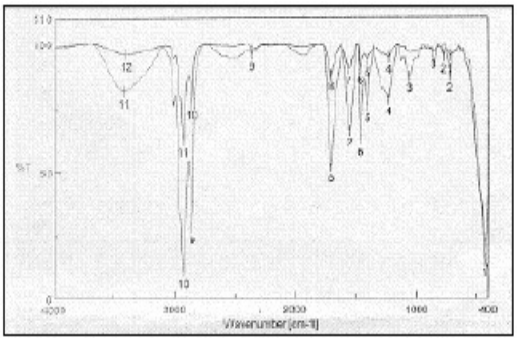
Graph 3: FTIR Spectrum of F18



Graph 4: FTIR Spectrum of F20

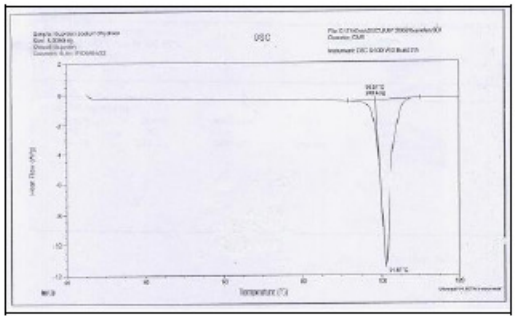
Graph 5: FTIR overlapped Spectrums F18 & F20



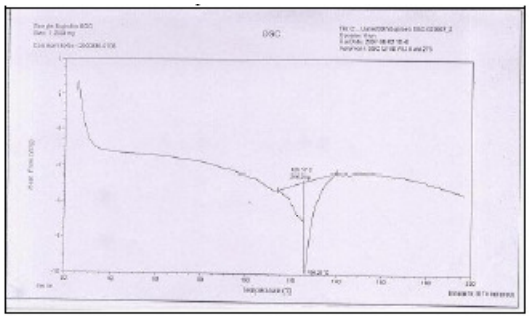


Differential Scanning Calorimetry (DSC): The DSC spectrums are mentioned in Graph 6, Graph 7 and Graph 8.

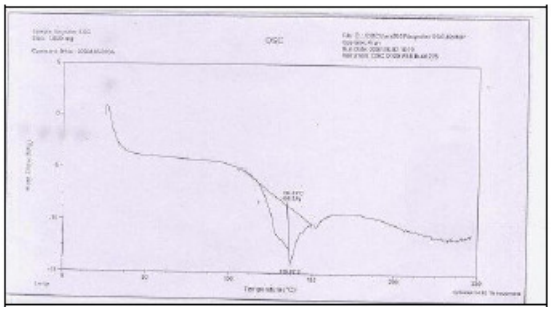
Graph 6: DSC studies of Drug



Graph 7: DSC studies of F18



Graph 8: DSC studies of F20



Stability Study results are given in Table 8 and Table 9.

Table 8: 1 Month Stability Study data of F18

Parameters	Assay (%)	Related substances	Dissolution		pH
			Time (min)	% Release	
25°C/60%RH	97.5	Nil	60	73.68	6.3
30°C/65%RH	96.66	Nil	60	73.07	6.2
40°C/75%RH	96.72	Nil	60	74.08	6.3

Table 9: 1 Month Stability Study data of F20

Parameters	Assay (%)	Related substances	Dissolution		pH
			Time (min)	% Release	
25°C/60%RH	101.3	Nil	60	94.53	6.3
30°C/65%RH	100.8	Nil	60	95.01	6.1
40°C/75%RH	101.0	Nil	60	95.95	6.3

DISCUSSION:

Preformulation studies were carried out on drug showed the Carr's Index was 25.4, which indicates satisfactory results.

The solubility trials gave two optimized drug fills which were selected for encapsulation. The evaluation parameters such as Average weight, Average fill weight of capsule, Uniformity of fill weight, Disintegration time, Capsule size, Hardness, in-vitro dissolution, Uniformity of dosage units (by weight variation), Assay and Compatibility studies were within the limit. It was shown that the formulations F18 and F20 containing Oleic acid, Water, Sodium Lauryl Sulphate and Propylene Glycol gave enhanced solubility and a clear solution. The FTIR spectra of pure drug and optimized drug fills was obtained and analyzed. The peaks obtained in the optimized drug fills were almost identical to those obtained for pure drug revealing that there was no interaction between drug and excipients used in drug fill formulations.

DSC studies showed that pure drug and optimized drug fill formulations are compatible. Stability studies are carried out at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH as per ICH guidelines. One month stability study data was collected. Compatibility studies done using IR, DSC and Identification by HPLC method indicated drug and excipients used in formulations were compatible. Packaging studies were carried out using PVC, Aluminium foil and HDPE containers. These formulations were kept for stability studies and results of stability indicate that packaging material is compatible with formulation.

The evaluation tests carried out complies with official standards. Thus we have succeeded in formulating stable formulation of soft gelatin capsules of Ibuprofen Sodium Dihydrate having adequate therapeutic efficacy.

CONCLUSION:

Soft gelatin capsules of Ibuprofen Sodium Dihydrate were prepared using various excipients like Solubilizing agents, Co-solubilizing agents, Solubility enhancers such Oleic acid, Propylene glycol, Water and Sodium Lauryl Sulphate etc.

The rank order of best formulation was F20 > F18.

Compatibility studies carried out using FTIR, DSC and HPLC showed the drug and Excipients were compatible.

Stability studies as per ICH guidelines showed soft gelatin capsules of ISD were stable.

Packaging studies carried out revealed that the formulation and packaging material has no interaction.

Thus, it may be concluded that soft gelatin capsules of Ibuprofen Sodium Dihydrate can be successfully prepared with existing machinery and technology which have a commercial viability, which will surely enhance patient compliance and have improved bioavailability.

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