Research Article **CODEN: IJRPJK** **ISSN: 2319 – 9563**

International Journal of Research in Pharmaceutical and Nano Sciences

Journal homepage: **www.ijrpns.com**

FORMULATION AND EVALUATION OF LOPERAMIDE LIQUISOLID COMPACTS

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ABSTRACT

Liquisolid Technique is a novel technique. It is used to improve the dissolution rate of the poorly water soluble drugs like Loperamide. The liquisolid compacts were prepared by using carrier, coating material and liquid medication. Liquisolid compacts refer to the formulations that are formed by conversion of liquid drugs, drug suspension or solution in non-volatile solvents into dry non-adherent, free flowing and compressible powder mixture. Hence, the liquisolid technology allows the conversion of liquid systems into solid drug delivery systems such as Tablets. The crystallinity of the newly formulated drug and the interaction between excipients were examined by X - ray Powder Diffraction (X - RD) and Fourier-Transform Infrared Spectroscopy (FTIR). Finally among various formulations of Loperamide liquisolid compacts, the optimal formulation of the batch F2, prepared with 2% Propylene glycol and 20mg Aerosil showed an increased dissolution rate of poorly water soluble Loperamide drug of about 85% drug release within 15 minutes. Loperamide, is a Piperidine derivative and it is used as an Anti- diarrheal agent.

KEYWORDS

Loperamide, Liquisolid compacts, Aerosil, X-RD, FT-IR and Dissolution profile.

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INTRODUCTION

In the formulation development process, solubility of active compound is one of the main criteria, to be considered before deciding the dosage form. Most of the hydrophobic drugs show very poor dissolution in the GIT, leading to erratic and incomplete drug absorption. Among the newly developed drugs which are meant for oral administration, around half exhibit solubility problem in water, which affect the formulation development process. Due to the many advantages associated with oral route, the poor solubility of

such drugs suffer with slow dissolution and poor bioavailability. The drugs belong to the Biopharmaceutical Classification System (BCS) of class II and IV shows very poor dissolution, leads to incomplete drug release from the formulation, increase in dose, large inter and intra - subject plasma concentration variation under both fed and fasted states, eventually leads to poor bioavailability.

Over past few decades, many techniques have been developed, to improve the solubility and dissolution of poorly soluble substances. Out of which the recent researches focus on liquisolid compact technique or powdered solution technique which is one of the successful tool to achieve the goal.

Liquisolid compacts are acceptably flowing and compressible powder forms of liquid medications. The liquid medication is the water insoluble drugs carried in suitable non - volatile solvents. Hence, the liquisolid technology allows the conversion of liquid systems into solid drug delivery system such as Tablets and this approach has been successfully applied in solubility and release enhancement of low dose poorly soluble drugs.

Loperamide is a Piperidine derivative, which is used as anti–diarrheal. It slows intestinal motility, inhibits peristalsis of intestinal wall musculature and intestinal contents and minimizes fluid and electrolyte loss. Loperamide is an opioid – receptor agonist, which acts on the μ - opioid receptors in the myenteric plexus of the large intestine.

MATERIAL AND METHODS

Loperamide was a gift sample from Maysa Labs Pvt. Ltd., Hyderabad, India. Propylene Glycol, Polyethylene Glycol 200, 300, 400, 600, Tween 20, Tween 80, Span 20, Span 80 were purchased from S.D Fine Chem Ltd., Chennai, Aerosil and Sodium Starch Glycolate were purchased from Saraswathi Enterprises, Chennai.

Liquisolid compacts of Loperamide were prepared by using Propylene Glycol as a solvent, Microcrystalline Cellulose as carrier, Aerosil as coating material and Sodium Starch Glycolate as disintegrant. Interactions between the drug and excipients were examined by FTIR. The dissolution studies for Loperamide liquisolid compacts formulation, marketed product and pure drug were carried out in pH - 1.2 HCl buffer as dissolution media.

METHODOLOGY

Solubility Studies

Determination of Solubility

Select the best non - volatile solvent system to dissolve Loperamide, solubility studies of Loperamide were performed in non - volatile solvents like Tween 20, Tween 80, Polyethylene Glycol 200, 300, 400, 600 and Propylene Glycol. Saturated solutions were prepared by adding excess drug to the solvents and shaking on automatic test tube shaking machine for 48 hrs, then allowed to settle for another 2 hrs and centrifuged at 2500 rpm for further settling of undissolved crystalline material. After centrifugation, the solutions were filtered through 0.45μm millipore filter, diluted with distilled water and analysed by UV – Visible spectrophotometer at a wavelength of 214 nm for their drug content against blank.

Calculation of Load Factor

In a liquisolid system, the amount of liquid retained by the carrier and coating materials depends on the excipient ratio (R), where R = Q/q, and it is defined as ratio between weights of carrier (Q) and coating materials (q) present in the formulation.

Preparation of a liquisolid system with an acceptable flow rate and compressibility is possible when a maximum amount of retained liquid of the carrier material is not exceeded and this characteristic amount of liquid is termed as Liquid load factor (L_f), where $L_f = W/Q$ and it is defined as weight ratio of the liquid medication (W) and carrier powder (Q) in the system.

To calculate the loading factor, Propylene Glycol was added to 10gm carrier material and blended for 1 min. The above procedure was repeated until a powder with acceptable flow rate was obtained.

Evaluation of Powder Blend (Pre Compression Parameters)

The prepared powder blend were subjected to evaluation as per in I.P. like Bulk density, Tapped density, Carr's index, Hausner's ratio and Angle of Repose.

Bulk density = Weight of sample in gm / volume occupied by the sample

Tapped density = Weight of sample in gm / Tapped volume

Compressibility index (Carr's index) = (Tapped density – Bulk density) / Tapped density x 100

Hausner's Ratio = Tapped density / Bulk density

Angle of Repose

To assess the flow property of powder, the angle of repose of the powder was determined by fixed funnel method. It can be calculated using the formula, tan θ = h/r, where h and r are the height and radius of the pile respectively.

Method of Preparation

Direct Compression Method

Loperamide drug was initially dispersed in the non - volatile solvent systems (Propylene Glycol, Polyethylene Glycol 400) termed as liquid vehicles with different drug : vehicle ratio.

Then a mixture of carrier (Microcrystalline Cellulose pH 102) was added to the above liquid by continuous mixing for a period of 10 - 20 mins in a mortar, until free flow is obtained.

To the above mixture, coating material (Aerosil powder) was added and mixed thoroughly. The amount of carrier and coating materials added were based on the R value.

To the above binary mixture, disintegrants like Cross Povidone, Sodium Starch Glycolate and other remaining additives such as glidant (Magnesium stearate) are added according to their application and mixed in a mortar.

The final blend was compressed by using 9 mm punch.

Evaluation of Liquisolid Tablets (Post Compression Parameters)

The prepared tablets were evaluated for hardness, friability, weight variation, drug content and disintegration time.

Hardness was determined by Monsanto Hardness Tester.

Friability was determined by Campbell Tablet Friability Tester.

Weight variation and Drug content were determined according to the standard procedures.

Disintegration time was determined by Campbell USP Disintegration Apparatus.

Dissolution Studies (*In vitro* Drug Release Studies)

Dissolution studies were performed for liquisolid tablets of different formulations, pure drug and marketed product. It was determined by using USP - type 2 (paddle type) apparatus under sink conditions. The dissolution medium was 900ml of 0.01M HCl, maintained at 37 ± 0.5°C at 50 ± 1 rpm to stimulate *in-vivo* conditions. The formulation prepared was subjected to dissolution tests for 2 hrs. Sample of about 5ml was withdrawn at predetermined time intervals (5, 10, 15, 30, 45, 60, 90 and 120 mins) and filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Samples were analysed at 214nm using LABINDIA UV – Visible spectrophotometer.

Comapatability Studies (FT-IR Studies)

This study was performed to know the compatability between the drug and excipients. The Potassium bromide disc method was used for the preparation of samples. The resultant disc was mounted in a suitable holder in Infrared spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1}. The resultant spectra were compared for any spectral changes.

Powder X – Ray Diffraction

Powder X – ray diffraction pattern of Loperamide, excipients, physical mixture and liquisolid formulation were studied using X – ray Diffractometer.

Stability Studies

The stability studies were performed according to the ICH guidelines by exposing the formulations F1 to F9 in their final packing mode to the temperature of 40 ± 2°C and relative humidity of 75 ± 5% using programmable environmental test chamber. At

appropriate time intervals of 1st, 2nd and 3rd month aliquots were withdrawn and analysed for change in drug content, hardness, friability, disintegration time and *in-vitro* drug release rate.

RESULTS AND DISCUSSION

Evaluation Parameters for Immediate Release Liquisolid compacts of Loperamide

Pre Compression Parameters

The values for Angle of Repose were found to be in the range of 28 - 32, Bulk densities and Tapped densities of various formulations were found to be in the range of 0.20 ± 0.006 to 0.25 ± 0.007 (g/cc) and 0.25 ± 0.006 to 0.28 ± 0.005 (g/cc) respectively. Carr's Index of the prepared blends fall in the range of 7.4% to 23.07%. From the result it was concluded that the powder blends had good fair flow properties and these can be used for tablet manufacture.

Post Compression Parameters

Hardness

Hardness of the three tablets of each batch was checked by using Monsanto Hardness Tester. The results showed that the hardness of the tablets was in the range of 3.0 to 4.5 kg/cm^2.

Weight Variation Test

Tablets of each batch was subjected to weight variation test, difference in weight and percent deviation was calculated for each tablet.

Friability

Tablets of each batch were evaluated for percentage friability and the datas were shown. The average friability of all the formulations lies in the range of 0.39% to 0.82% which was less than 1% as per official requirement of IP indicating a good mechanical resistance of tablets.

In-vitro Disintegration Time

The results showed that the Disintegration time of prepared tablets were in the range of 3 to 5 mins.

In-vitro Dissolution Studies

Finally, Tablets were evaluated for *in-vitro* dissolution studies in stimulated gastric fluid and the results were shown.

Formulations F1 to F9 showed drug release in the range of about 51.52 % to 98.27% with 4% of Sodium Starch Glycolate, various concentration of Aerosil and Propylene Glycol. Out of these formulations, the tablets of batch F2 prepared with 2 % Propylene Glycol and 20mg Aerosil showed 85% of drug release within 15 mins.

Powder X –ray Diffraction

Powder X –ray Diffraction pattern of Loperamide, excipients, physical mixture and liquisolid formulation were studied using X – ray Diffractometer.

Stability Studies

Stability studies were carried out for the selected formulation F2 and the results were shown below. The result showed that there was no significant difference in the drug content, disintegration time, hardness and friability at various sampling intervals. The *in-vitro* dissolution profiles were super impossible, which confirms the stability of the product.

Loperamide liquisolid compacts were formulated as immediate release tablets using sodium starch glycolate as disintegrants in increased concentration by Direct Compression Method. Finally, the data suggested that the Loperamide tablets were evaluated for post compression parameters suggested that hardness, thickness, weight variation, friability were in acceptable limit with good handling properties. All the Loperamide liquisolid compacts formulations were rapidly disintegrates in less than 5 mins and they showed the drug content of more than 92 %.

Table No.1: Evaluation Parameters

S.No	Formulations	Weight Variation	Hardness kg/cm2	Disintegration time (min)	Friability%	% of Drug content (%W/W)
1	F1	323 ± 3.0	4.5 ± 0.02	3	0.79	96.5
2	F2	292 ± 2.5	3.0 ± 0.05	4	0.65	98.2
3	F3	302 ± 3.11	3.0 ± 0.01	4	0.53	92.9
4	F4	327 ± 4.7	4.0 ± 0.03	3	0.56	94.00
5	F5	263 ± 2.14	4.5 ± 0.04	3	0.77	95.9
6	F6	243 ± 3.23	3.5 ± 0.03	5	0.71	97.43
7	F7	315 ± 7.43	3.5 ± 0.01	4	0.39	92.24
8	F8	333 ± 3.56	3.0 ± 0.01	4	0.48	90.09
9	F9	302 ± 1.98	3.5 ± 0.03	3	0.82	94.89

Table No.2: *In vitro* % Drug Release Profile Data of Loperamide Liquisolid Compacts

Time(min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
5	34.50±0.9	40.98±1.0	42.06±1.09	23.00±0.9	45.06±0.9	33.02±1.20	29.07±0.8	30.96±0.08	24.43±0.8
10	37.44±1.2	52.89±1.0	49.0±1.04	50.10±0.7	49.92±1.4	34.93±1.12	31.01±0.9	33.98±0.6	30.67±09
15	47.66±0.8	86.81±1.0	54.40±1.20	52.66±0.9	51.09±1.3	44.88±1.05	32.65±0.9	39.25±1.01	49.05±0.9
30	52.90±0.8	89.76±0.9	58.99±1.15	58.50±1.1	53.22±1.21	50.56±1.04	38.36±1.24	40.61±1.04	53.01±0.7
45	72.89±1.10	90.50±1.0	69.35±1.6	60.01±0.9	59.24±1.02	52.68±1.09	40.74±1.02	44.17±0.9	58.90±1.00
60	74.38±0.7	96.57±1.1	85.76±0.9	67.71±0.5	59.38±1.3	60.09±1.10	49.27±1.10	50.26±0.8	61.96±1.03
90	85.23±0.4	97.8±1.00	87.81±1.12	72.30±0.3	60.33±0.7	67.8±1.03	54.93±1.42	50.37±1.12	69.87±0.9
120	86.79±1.3	98.27±0.9	88.44±0.9	83.4±0.9	66.22±0.9	70.31±1.32	55.48±1.3	51.52±1.01	72.08±0.9

Table No.3: Optimized Formula compared with the Pure Drug and Marketed Product

S.No	Time (min)	Optimized Formula F2	Marketed drug	Pure drug (Loperamide)
1	0	0	0	0
2	5	40.98	18.8	9.99
3	10	52.89	35.83	10.5
4	15	86.81	54.57	15.21
5	30	89.76	60.64	17.18
6	45	90.5	79.66	23.98
7	60	96.57	84	30.2
8	90	97.8	98	33.45
9	120	98.21	102.89	55.01

Table No.4: Stability Studies at Temperature 40 ± 2°C and Relative Humidity 75 ± 5%

S.No	Time Intervals	Drug Content %
1	Initial	99.2
2	1 Month	98.90
3	2 Months	98.07
4	3 Months	97.84

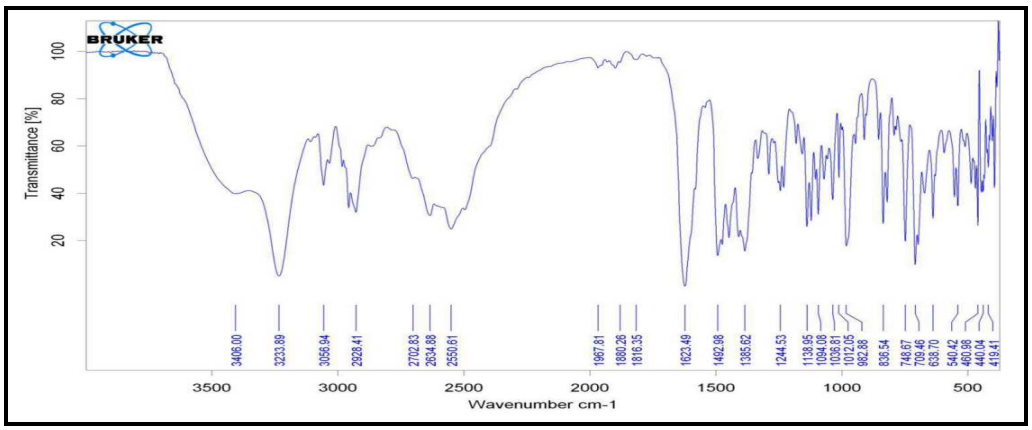

Figure No.1: FT-IR Studies of Pure Drug: Loperamide

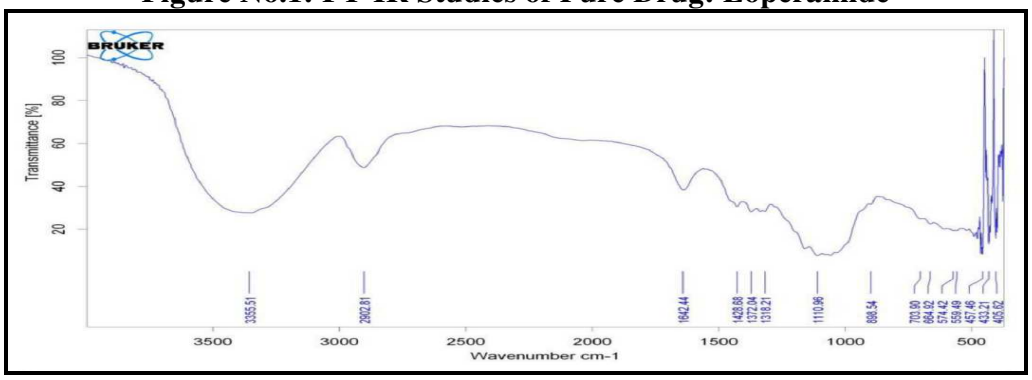

Figure No.2: FT-IR Spectra of Optimized Formula: (F2)

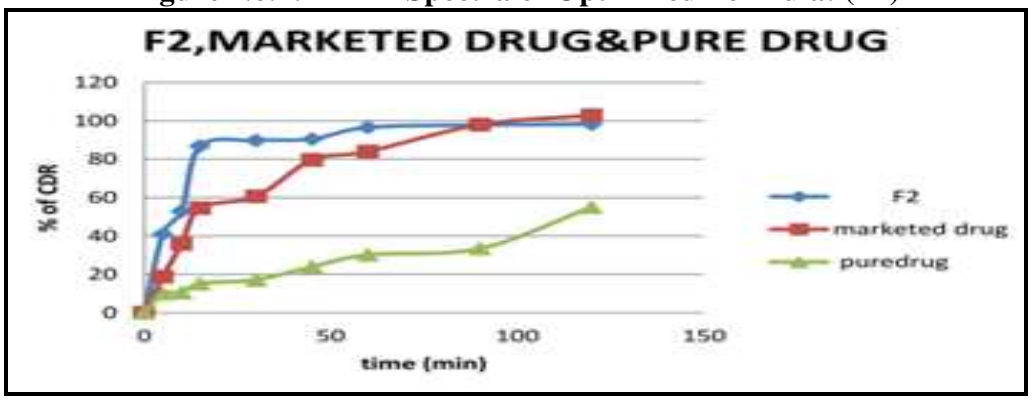

Figure No.3: Comparison of F2, Marketed Drug and Pure Drug

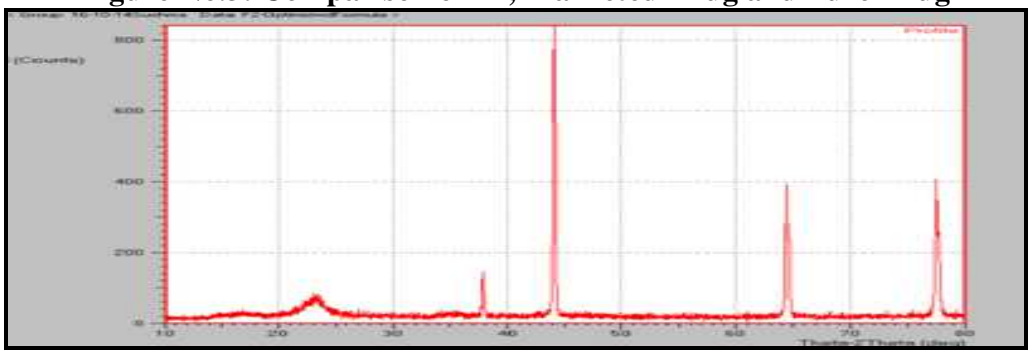

Figure No.4: Optimized Formula F2

CONCLUSION

The major problem in oral drug formulations is low and enteric bioavailability, which mainly results from poor aqueous solubility. Liquisolid compacts is the most attractive processes to improve solubility of poorly soluble drugs. Here, the solubility of Loperamide is enhanced by liquisolid compacts with propylene glycol as liquid medication. Among the various liquisolid compacts were prepared, the formulation F2 with propylene glycol 2%, shows faster dissolution rate. Accelerated stability studies were carried out for selected formulations F2 which showed no significant difference in the drug content, disintegration time, hardness, friability and *in-vitro* dissolution studies which confirms the stability of the product.

ACKNOWLEDGEMENT

The authors very thankful to Department of Pharmaceutics, RVS College of Pharmaceutical Sciences for all research facilities provided to carry out this work.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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