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FORMULATION AND EVALUATION OF LOPERAMIDE LIQUISOLID COMPACTS

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ABSTRACT

Loperamide is an anti diarrhoeal drug administered orally. It is a poorly water soluble drug with low oral bioavailability. The present study was aimed at increasing solubility of Loperamide and thus enhance its dissolution rate by a novel technique called liquisolid system. Liquisolid compacts were prepared by propylene glycol, Micro crystalline cellulose and Aerosol as solvent, carrier and coating material respectively in different ratios. By performing FTIR it was confirmed that there was no incompatibility between the drug and other excipients. Flow properties of the drug were measured and found to be within pharmacopoeal limits. Taking in vitro drug release, final formulation weight, drug content and flow properties into consideration, formulation F2 was optimized. XRD patterns show that the drug in the formulation got transformed to amorphous form. The optimized formulation showed good dissolution rate when compared to marketed formulation and pure drug. So the liquisolid technique was proved to be efficient in improving dissolution properties of Loperamide.

Keywords: Liquisolid compacts, Loperamide, Aerosol, in-vitro release

INTRODUCTION

Even though there are many routes of administration of drugs, oral delivery of drugs remain significant due to high patient compliance. Among orally delivered dosage forms, tablets are most widely preferred as they are easy to administer. But the drug should be in solution form when it reaches gastrointestinal fluid for absorption. BCS class II drugs which are poorly water soluble cannot dissolve in the Gastro intestinal fluids thus resulting in poor absorption. Unfortunately most of the newly discovered drugs suffer from poor solubility. In order to improve solubility and thus bioavailability of such drugs, various techniques have been adopted. Among them micronization,[1] Complexation,[2] ball milling,[3] solid dispersions,[4] self emulsifying drug delivery systems[5] are some of the techniques. Recently liquisolid system, a new technique showed promising results in enhancing dissolution characteristics of poorly soluble drugs.[6] Liquisolid system is dry, free flowing, non-adherent, compressible powder mixtures converted from liquid drugs in non-volatile solvents with selected carriers and coating materials.[7] The drug is first dissolved in a non-volatile solvent and is converted to dry form by using carrier and coating material. The appropriate amounts of carrier and coating material required for obtaining free flow of powder is calculated by mathematical model given by Spireas and Bolton.

Loperamide is a BCS class II drug which is used to decrease the frequency of diarrhoea in gastroenteritis, inflammatory bowel disease. It acts as an agonist on the μ-opioid receptors in the myenteric plexus of the large intestine thereby increasing the residence time of substances in the intestine and thus allow more water to be absorbed out of the fecal matter. Its solubility and Oral bioavailability were reported to be 0.00086 mg/ml and 0.3% respectively. So it is necessary to improve its dissolution rate in Gastro intestinal fluid so as to improve its bioavailability.

The aim of the present study is to formulate Loperamide liquisolid compacts using Propylene glycol, Micro crystalline cellulose (MCC), Aerosol, Sodium starch glycolate as vehicle, carrier, coating material and super disintegrant respectively so as to improve solubility of Lurasidone and thus it's dissolution rate.

MATERIALS AND METHODS

Materials: Loperamide was obtained as gift sample from Aurobindo laboratories Pvt. Ltd. (Hyderabad, India). MCC, Propylene Glycol, Aerosol and Sodium starch glycolate were supplied by S D Fine chemicals (Hyderabad, India).

Methods

Solubility studies: Solubility studies of Loperamide were conducted by placing an excess amount of the drug in a 1ml eppendorf tube containing 1ml of solvent (Table 1). The mixture was vortexed using cyclone mixer (REMI CM 101DX, REMI Equipment, Mumbai, India) and kept at 25 ^{0}c in orbital shaker (CL 24, Remi Electrotech Ltd., Mumbai, India) for 48 hrs to facilitate the solubilisation. Then the samples were centrifuged at 2000 rpm for 15 min to remove undissolved drug. The supernatant was diluted with methanol and absorbance was measured by UV-VIS double beam spectrometer (LAB INDIA) at 214 nm.[8]

Calculation of load factor : The amount of liquid retained in a liquisolid system by the carrier and coating materials depend on the excipient ratio (R) while maintaining acceptable flow and compression properties. The ratio between the weights of carrier (Q) and coating materials (q) present in the formulation gives the excipient ratio, R (Q/q) of a powder. Liquisolid system with an acceptable flow rate and compressibility is possible to prepare when a maximum amount of retained liquid of the carrier material is not exceeded. This specific amount of liquid is called as liquid load factor (Lf). The weight ratio of the liquid medication (W) and carrier powder (Q) in the system gives the liquid load factor, Lf (W/Q). Propylene glycol (liquid medication without drug) was added to 10 g carrier material and blended for 1 min to calculate the load factor. This procedure was repeated until a powder with acceptable flow rate was obtained.[9]

Flow properties of liquisolid powders: Flow properties of the liquisolid powder formulations were studied by determining angle of repose, compressibility index, Hausner ratio and compressibility index. To measure angle of repose, funnel and cone method was employed. Above a graph paper placed on a horizontal surface a funnel was fixed at a given height (H). The powders were dropped through the funnel until the apex of the conical pile touches he tip of the funnel. The height of the pile and mean radius of the base of the conical pile were determined and substituted in the formula $\theta = \tan^{-1} h/r$, where θ is angle of repose.[10]

Powder X-Ray diffraction (PXRD: The PXRD patterns of pure drug and optimized Loperamide liquisolid powder formulation were obtained using X-ray diffractometer (Eindhoven, Netherlands). The measurement was done using Cu-Kα radiation, nickel filtered graphitic monochromator at 40 kV voltage and 30 mA current and the scanning rate employed was 10 min^{-1}.[9]

Preparation of liquisolid compacts and tablet: Loperamide was dissolved in propylene glycol which is used as a liquid vehicle to prepare the drug solution. To the liquid medication, the mixture of carrier coating materials (MCC as the carrier and Aerosol 200 as the coating material) was added and blended in a porcelain mortar avoiding excessive trituration and particle size reduction. To it, 4 % of disintegrant (Sodium starch glycolate) was added and mixed thoroughly. The final resultant mixture was compressed into tablets. [7] The formulation chart was shown in Table 3.

Evaluation of liquisolid tablets: The prepared liquisolid compacts were evaluated for hardness, friability, weight variation, drug content and disintegration time. Hardness was determined by the Monsantto hardness tester, friability by a digital tablet friability tester (Roche friabilator). The disintegration time was measured using a USP disintegration tester (Electrolab).[11]

Dissolution Studies: Dissolution studies were carried out on pure drug, marketed formulation and optimized formulation using USP Type-II (Paddle type) apparatus. The dissolution was studied in 900 ml of 0.1N HCl with 50 rpm paddle speed for 2 hr. 5 ml aliquots were withdrawn at predetermined time intervals and were replaced by an equal amount of fresh dissolution medium. The withdrawn aliquots were filtered through 0.45 mm filter paper and were analysed for drug content by UV-VIS spectrophotometer (UV-3200, Labindia, India) at 214 nm.[12, 13]

FTIR Spectroscopy: FTIR studies were done on optimized formulation and pure drug using FTIR spectrophotometer. The samples were mixed with

KBr in 1:2 ratio and was compressed into discs using KBr pellet press. IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1}.

Stability studies: The optimized liquisolid formulation was subjected to accelerated stability studies at 40° C and 75% ± 5% RH as per ICH guidelines for a period of 3 months. After 90 days, the samples were analysed for in-vitro release and drug content.[14,15]

RESULTS AND DISCUSSION

Vehicle selection:
The solubility of Loperamide was determined in various solvents which was shown in Table 1. The solubility of the drug contributes to molecular dispersion in a non volatile solvent which improves the dissolution rate. Considering the solubility data, Propylene glycol was selected as the vehicle for Loperamide.

Flow properties of liquisolid powders: The values of angle of repose, bulk density, tapped density, carr's Index for all the liquisolid powder formulations were determined. From the results it was confirmed that all the powder blends had good to fair flow properties and these can be used for tablet manufacture. The results were shown in Table 2.

Hardness, Friability, weight variation, disintegration time, drug content: The results of Hardness, Friability, weight variation, disintegration time, drug content of all the tablets were shown in Table 4. Hardness test showed an average hardness of liquisolid tablets ranging from 3.0 to 4.5 Kg/cm^2. The percentage friability for all formulations was found to be below 1%, indicating that the friability is within the prescribed limits. Disintegration time was found to be in the range of 3 to 5 min. All prepared tablets complied with the pharmacopoeial specifications for the weight variation and drug content.

In-Vitro Dissolution Studies: In-vitro drug release studies were performed in 0.1N HCl for all the prepared formulations by using USP dissolution Type II apparatus (Paddle method). The drug release profile graphs for all the formulations were shown in Figure 2. *In-vitro* dissolution studies showed that the formulation containing increased amount of carrier material showed increased drug release rate. It was observed from the results that there is a relationship between the powder excipient ratio and in-vitro drug release. Liquisolid compacts with low *R*-values showed relatively poor dissolution compared to liquisolid compacts with high R-values. Among all the formulations, F2 showed 98.27% of drug release which may be due to the presence of more amount of carrier material.

Optimization of Loperamide liquisolid compacts: Among all the prepared formulations, formulation F2 was optimized as it showed good flow properties, optimum final formulation weight, evaluation parameters and highest in-vitro drug release as shown in Tables 2, 3, 4 and Figure 2 respectively. Optimized Loperamide liquisolid formulation had shown good in-vitro drug release when compared with pure drug and marketed tablet as shown in Figure 3.

FTIR: FTIR studies were conducted to determine compatibility between drug and excipients. FTIR spectra and characteristic peaks of pure drug Loperamide and optimized Liquisolid formulation were obtained and were shown in Figure 1. Loperamide FTIR spectra showed characteristic peaks at 3423.36 cm^{-1}, 2843.42 cm^{-1}, 1614.49 cm^{-1}, 1461.89 cm^{-1}, 1319.78 cm^{-1}, 1277.62cm^{-1}. All the characteristic peaks of Loperamide were found and no new bands were observed in the FTIR spectrum of the optimized liquisolid formulation. The FTIR studies revealed that there was no considerable interaction between the drug and all other ingredients in the optimized Loperamide liquisolid formulation.

Powder X-Ray diffraction: PXRD analysis was used to assess the degree of crystallinity of the liquisolid constituents. Loperamide showed major peaks at 2θ values of 16, 20, 44, 65, 78 (Figure 4). Analysis of PXRD patterns of the optimized formulation indicated that the degree of crystallinity of liquisolid compacts was decreased by the addition of excipients to the formulation. A fall in degree of crystallinity means an improvement in the amorphousness of a sample. So, with the increase in amorphous nature of the drug with suitable excipients led to improved dissolution release profile.[6]

Stability studies: The dissolution release profile of optimized liquisolid formulation before and after temperature sensitivity studies was determined and compared. The similarity factor was found to be greater than 50, which indicates good similarity of dissolution profiles. When drug content, friability, hardness and disintegration of optimized liquisolid compacts after storage were compared with before storage using paired t-test, it indicated an insignificant ($p > 0.05$) difference which is shown in Table 5. [16,17]

CONCLUSION

For improving the dissolution of a poorly soluble drug like Loperamide, the liquisolid technique was found to be a promising approach. The dissolution of Loperamide was increased in liquisolid formulation compared to pure drug and marketed product. PXRD spectrum indicated that there was no change in the drug got transformed to amorphous state and FTIR spectrum indicated that there were no interactions between the drug and excipients. Increase in dissolution rate may be due to increased wetting and increased surface area of the particles.

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Table 1. Solubility of Loperamide in different solvents

Solvent	Solubility (mg/ml)
PEG 200	73.26
PEG 400	75.59
PEG 600	64.29
Tween 20	68.34
Tween 80	71.95
Propylene glycol	149.65

PEG – Polyethylene glycol

Table 2. Flow properties of liquisolid powders

Formulation	Angle of repose	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
F1	28 ± 0.21	0.22 ± 0.02	0.25 ± 0.05	12.53 ± 0.12	1.13 ± 0.11
F2	30 ± 0.20	0.25 ± 0.03	0.27 ± 0.01	7.40 ± 0.29	1.08 ± 0.23
F3	29 ± 0.25	0.22 ± 0.05	0.25 ± 0.01	12.53 ± 0.19	1.13 ± 0.25
F4	28 ± 0.12	0.23 ± 0.01	0.26 ± 0.03	12.69 ± 0.17	1.13 ± 0.12
F5	27 ± 0.16	0.22 ± 0.07	0.26 ± 0.07	16.34 ± 0.21	1.18 ± 0.16
F6	28 ± 0.30	0.23 ± 0.09	0.25 ± 0.04	8.00 ± 0.15	1.08 ± 0.12
F7	32 ± 0.20	0.25 ± 0.01	0.28 ± 0.01	10.74 ± 0.32	1.12 ± 0.20
F8	30 ± 0.39	0.22 ± 0.03	0.27 ± 0.04	18.51 ± 0.24	1.22 ± 0.24
F9	28 ± 0.45	0.20 ± 0.04	0.26 ± 0.02	23.07 ± 0.31	1.30 ± 0.11

Table 3. Formulation of Loperamide Liquisolid Compacts

Formulation	Drug conc. in PG (% w/w)	R	L_f	MCC (mg)	Aerosol (mg)	Formulation weight (mg)
F1	2	5	0.225	300	60	425
F2	2	10	0.221	210	21	300
F3	2	20	0.21	200	10	290
F4	4	5	0.232	400	80	540
F5	4	10	0.201	300	30	400
F6	4	20	0.242	250	25	340
F7	6	5	0.233	350	70	500
F8	6	10	0.222	250	25	350
F9	6	20	0.212	200	10	280

Excipient ratio, R=Q/q. Q, weight of carrier; q, weight of coating material
Liquid load factor, L_f = W/Q . W, weight of liquid medication

Table 4. Evaluation Parameters

Formulations	Weight Variation	Hardness kg/cm^2	Disintegration time (min)	% Friability	% Drug content (% w/w)
F1	323 ± 3.0	4.5 ± 0.02	3	0.79	96.5
F2	292 ± 2.5	3.0 ± 0.05	4	0.65	98.2
F3	302 ± 3.11	2.5 ± 0.01	4	0.53	92.9
F4	327 ± 4.7	4.0 ± 0.03	3	0.56	94.00
F5	263 ± 2.14	4.5 ± 0.04	3	0.77	95.9
F6	243 ± 3.23	3.5 ± 0.03	5	0.71	97.43
F7	315 ± 7.43	3.0 ± 0.01	4	0.39	92.24
F8	333 ± 3.56	3.0 ± 0.01	4	0.48	90.09
F9	302 ± 1.98	3.5 ± 0.03	3	0.82	94.89

Table 5. Stability data of optimized S-SNEDDS formulation as per ICH guidelines.

Time (min)	% cumulative drug release	
	Initial	After storage at 40˚C/75 ± 5% RH for 90 days
0	0	0
5	40.98 ± 3.23	41.82 ± 3.12
10	52.89 ± 4.05	58.21 ± 4.48
15	68.81 ± 6.22	69.62 ± 5.82
30	72.76 ± 5.87	71.91 ± 5.63
45	83.50 ± 6.43	82.42 ± 6.32
60	90.57 ± 5.82	88.13 ± 4.42
90	95.80 ± 6.18	94.11 ± 5.98
120	98.27 ± 4.69	97.85 ± 4.98
Physical factors	**Initial**	**After storage at 40˚C/75 ± 5% RH for 90 days**
Drug content (% w/w)	98.2 ± 3.29	97.7 ± 4.12
	$f_2 > 50$, *p > 0.05	

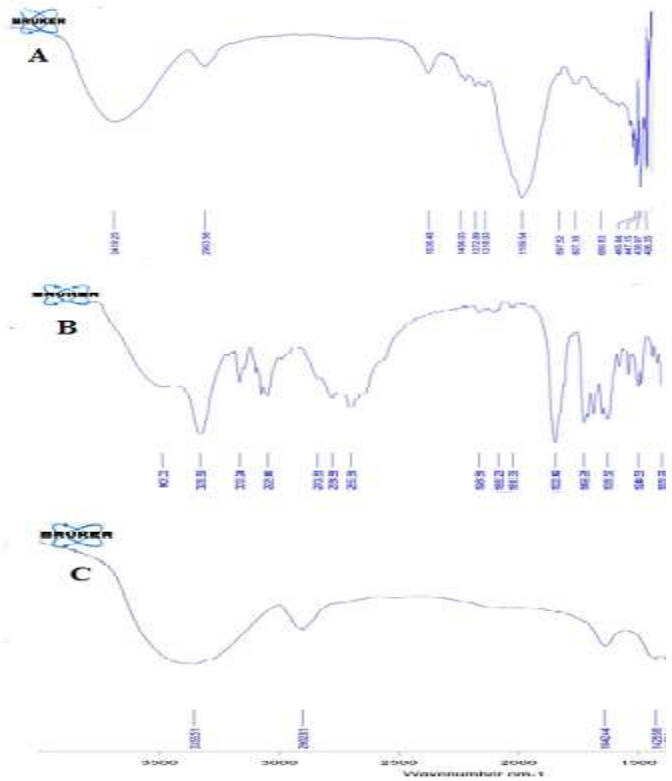

Figure 1: FTIR spectra of (A) Loperamide pure drug (B) Optimized formulation (C) MCC

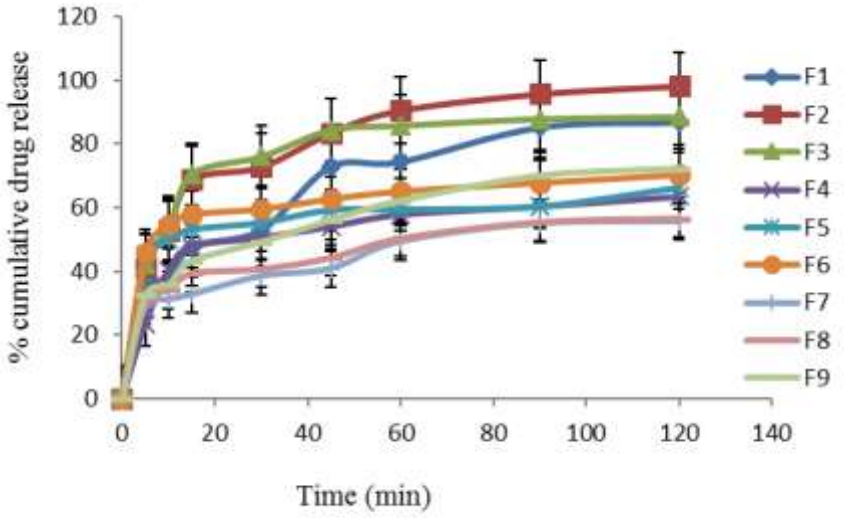

Figure 2: In-vitro release profiles of all the formulations

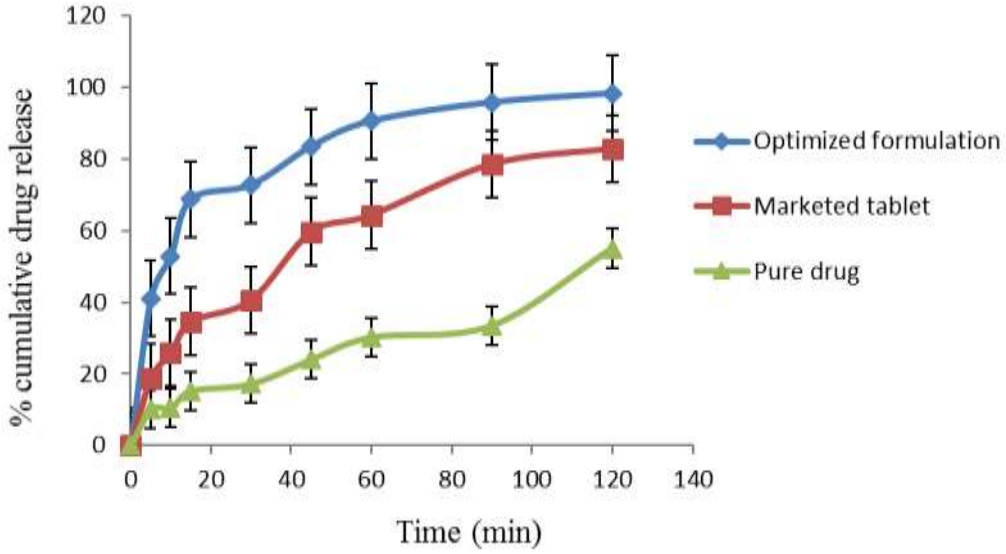

Figure 3: Comparative in-vitro release profiles of Loperamide pure drug, marketed tablet and optimized formulation

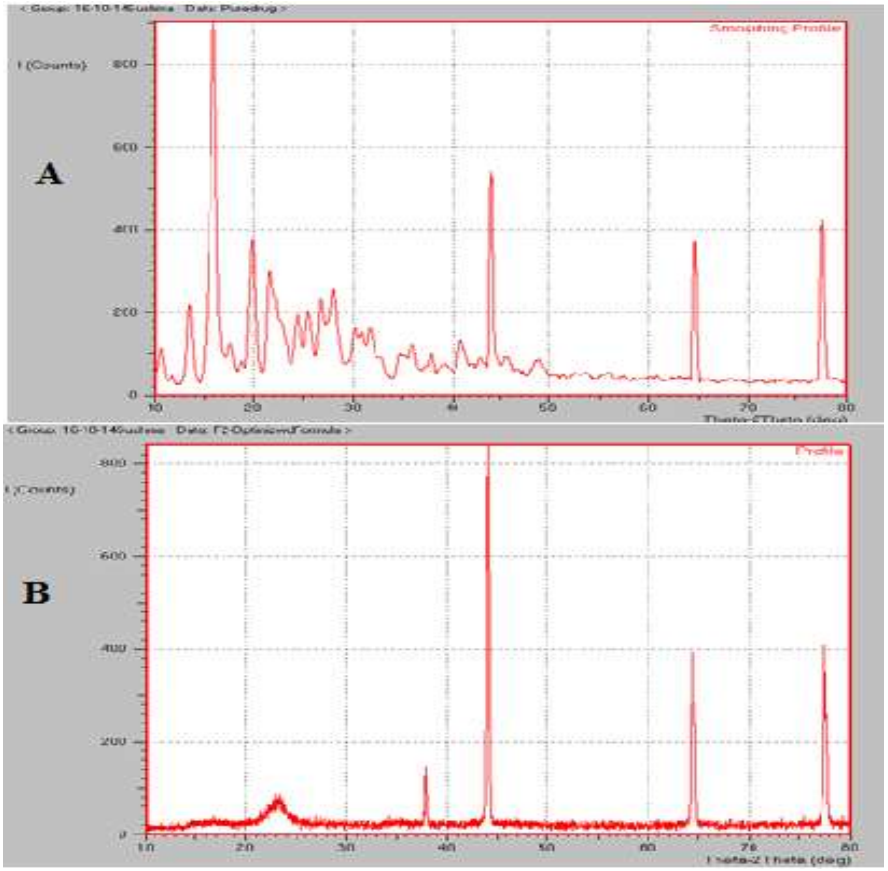

Figure 4: PXRD spectra of (A) Loperamide pure drug (B) Optimized formulation

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