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Research Article

Enhancement of Loperamide Dissolution Rate by Liquisolid Compact Technique

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Abstract

Purpose: The aim of present study was to improve the dissolution rate of poorly soluble drug Loperamide (LPM) by liquisolid compact technique.

Methods: Liquisolid compacts of LPM were prepared using Propylene glycol (PG) as a solvent, Avicel pH 102 as carrier, Aerosil as coating material and Sodium Starch Glycolate (SSG) as superdisintegrant. Interactions between the drug and excipients were examined by Fourier Transform Infrared (FTIR) spectroscopy. The dissolution studies for LPM liquisolid formulation, marketed product and pure drug were carried out in pH 1.2 HCl buffer as dissolution media.

Results: Results confirmed the absence of chemical interactions between the drug and excipients. From the solubility studies, it was observed the LPM was highly soluble in PG thereby it was selected as a solvent. The dissolution efficiency of LPM at 15 min was increased from 9.99 % for pure drug and 54.57% for marketed product to 86.81% for the tablets prepared by liquisolid compact technique. Stability studies showed no significant change in percent cumulative drug release, hardness, disintegration time, friability and drug content for 3 months.

Conclusion: Formulation F2 showed significant increase in dissolution rate compared to the marketed product at pH 1.2 where LPM is largely absorbed. Around 90% of the drug was released from F2 in 30 min compared to the marketed product and it might be due to the increased wetting and surface area of the particles. Hence, the liquisolid compact technique appears to be a promising approach for improving the dissolution rate of poorly soluble drug.

Introduction

The most preferred route of drug administration is oral route due to its ease, patient compliance and low production cost. The drug must be presented in solution form for absorption through gastro intestinal tract (GIT) when given orally. In the case of poorly soluble drugs, solubility is an important parameter and dissolution is the rate limiting step in absorption process.[1] Generally, drugs with aqueous solubility of less than 100 µg/mL show dissolution limited absorption and incomplete absorption from GIT of humans.[2] Recent advancements in drug discovery have led to the discovery of large number of active compounds and however, nearly 40 % of the new compounds are poorly soluble or insoluble in water which leads to ineffective absorption and therapeutic failure.[3]

It is well known that the most of the pipeline drugs are poorly water soluble or water insoluble in nature, hence it is a challenging aspect for both researchers and industries to develop drugs with water soluble characteristic. There are various techniques reported to improve the dissolution of poorly water soluble or water insoluble drugs like microinization,[4,5] complex formation with β-Cyclodextrins,[6] eutectic mixtures,[7] spray drying technique[8] and recently liquisolid technique has shown promise for improved dissolution. The concept behind the liquisolid system was developed from powdered solution technology and it can be used to formulate the liquid medication. In this technique, insoluble or poorly soluble drugs are dispersed or incorporated into suitable non-volatile solvent and converted to dry, free flowing and compressible solids suitable for tableting or encapsulation using carrier and coat materials. Now the drug is present in liquid medicament as solubilised or dispersed state, thereby the dissolution and bioavailability might be enhanced due to the increased wetting and surface area.[9]

LPM is an opioid receptor agonist and acts on µ-opioid receptors located in myenteric plexus of the large intestine and used for treatment of different types of diarrhoeal conditions.[10] The drug LPM comes under BCS class II drugs[11] and has low solubility profile.[10] Hence, it is necessary to improve the dissolution rate so as to improve the bioavailability of drug. Various techniques such as emulsion solvent diffusion technique,[12] β-Cyclodextrin inclusion complex[13] and oral disintegrating tablets[14] were reported previously. The

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present study was aimed to improve the dissolution rate of LPM using liquisolid compaction technique.

Materials and Methods

Materials

LPM was obtained from Maysa labs Pvt. Ltd., India. MCC pH 102, Aerosil and SSG were purchased from Saraswathi enterprizes, India and remaining all the chemicals were obtained from S.D Fine Chem Ltd., India. Marketed product Imodium® (Ethnor Ltd., India) was purchased from local pharmacy.

Solubility studies

To select the best non-volatile solvent system to dissolve LPM, solubility studies of LPM were performed in non-volatile solvents like Tween 20, Tween 80, Polyethylene glycol (PEG) 200, PEG 400, PEG 600 and PG. Saturated solutions were prepared by adding excess drug to the solvents and shaking on automatic test tube shaking machine (IKA India Pvt. Ltd.) for 48 h, then allowed to settle for another 2 h and centrifuged (REMI, India) at 2500 rpm for further settling of undissolved crystalline material. After centrifugation, the solutions were filtered through 0.45 µm Millipore filter, diluted with distilled water and analyzed by UV-Visible spectrophotometer (Lab India 1700 UV-Visible spectrophotometer, India) at a wavelength of 214 nm against blank.[15]

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) i.e. R=Q/q and it is defined as the ratio between the weights of carrier (Q) and coating materials (q) present in the formulation.[16] 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). The L_f is defined as the weight ratio of the liquid medication (W) and carrier powder (Q) in the system (i.e., L_f=W/Q).[17] To calculate the loading factor, PG was added to 10 gm carrier material and blended for 1 min. The above procedure was repeated until a powder with acceptable flow rate was obtained.

Flow properties of liquisolid powder

To assess the flow property of powder, the angle of repose of the powder was determined by fixed funnel method. The height of the funnel was adjusted so that the tip of the funnel just touches the apex of the heap of the powder above a graph paper that was placed on a flat horizontal surface. Accurately weighed powder blend was allowed to flow through the funnel freely on to the surface of the graph paper to form a cone shaped file. The diameter of the powder cone (d) and the height (h) of the pile were noted. From the diameter, radius (r) was calculated. The angle of repose was calculated using the following formula, $\tan \alpha = h/r$, α is the angle of repose.[15]

FTIR studies

This study was performed to know the compatibility between the drug and excipients. The potassium bromide disc method was used for the preparation of samples and about 5 mg of sample was mixed thoroughly with 100 mg potassium bromide IR powder and compacted under vacuum at a pressure of about 12,000 psi for 3 min. The resultant disc was mounted in a suitable holder in Shimadzu IR spectrophotometer and the IR spectrum was recorded from 4000 cm^{-1} to 400 cm^{-1}. The resultant spectra were compared for any spectral changes.[18]

Preparation of liquisolid tablets of LPM and liquid compacts

The liquisolid compacts were prepared according to the method described by Spireas and Bolton.[9] The drug LPM was dispersed in PG to prepare drug solution. Then the mixture of carrier (MCC pH 102) and coating material (Aerosil) was added to the above liquid medicament by continuous mixing for about 10 to 20 min in a porcelain mortar avoiding excessive trituration and size reduction. To the above mixture, superdisintegrant SSG was added and mixed thoroughly. The final blend was compressed into tablets by RIMEK rotary tablet punching machine using 9 mm punch [Table 1].[15]

Table 1. Formulation of LPM Liquisolid Compacts

Formulations	Drug Concentration in PG (% w/w)	R[#]	L_f[$]	MCC (mg)	Aerosil (mg)	SSG	Total Tablet Weight (mg)
F1	2	19.3	0.22	300	15.5	40	380
F2	2	10.5	0.25	210	20	40	320
F3	2	20	0.24	200	10	40	300
F4	4	5.6	0.35	225	40	40	330
F5	4	11	0.36	220	20	40	310
F6	4	9.4	0.34	235	25	40	320
F7	6	10.8	0.28	260	24	40	340
F8	6	20	0.30	250	12.5	40	330
F9	6	16	0.33	240	15	40	310

[#] 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, Q= Weight of carrier

Evaluation of liquisolid tablets

The prepared tablets were evaluated for hardness, friability, weight variation, drug content and disintegration time. Hardness was determined by Pfizer hardness tester, friability by a tablet friability tester and disintegration time by a USP disintegration tester.[18,19]

Weight variation and drug content were determined according to the standard procedures. [20,21]

Dissolution Studies

Dissolution studies were performed for liquisolid tablets (F1, F2 and F3), pure drug and marketed product (Imodium®). The USP paddle method (Electro lab TDT-06N USP dissolution test apparatus, India) was used for *in-vitro* dissolution studies. It was performed in dissolution media i.e. pH 1.2 HCl buffer solution and rotation of paddle was set at 50 ± 1 rpm to simulate *in-vivo* conditions. The amount of LPM was 2 mg in all formulations. The dosage forms were placed in 900 ml of dissolution medium and maintained at 37 ± 0.5°C. At appropriate time intervals (5, 10, 15, 30, 45, 60, 90 and 120 min), 5 mL of sample was withdrawn and filtered through 0.45 µm Millipore filter. The samples were analyzed at 214 nm using UV-Visible spectrophotometer. The mean value of 6 determinations was used to calculate the drug release from its formulation.

Stability studies

The stability studies were performed according to the ICH guidelines. From the results of *in-vitro* drug release studies, F2 was selected and exposed in its final packing mode to the temperature of 40 ± 2°C and relative humidity of 75 ± 5% using programmable environmental test chamber (EIE Instruments). At appropriate time intervals of 1st, 2nd and 3rd month, aliquots were withdrawn and analyzed for change in drug content, hardness, friability, disintegration time and *in-vitro* drug release rate.[22]

Results and Discussion

LPM is used for the treatment of different diarrhoeal conditions and has an absorption window in the upper gastrointestinal tract. Hence, the objective of this study was to enhance the dissolution of LPM at pH values that simulate the gastric conditions so as to improve gastric absorption.

Compatibility studies

The IR spectrum of pure drug exhibits characteristic absorption peaks at 3423 cm^{-1} (OH str), 2843 cm^{-1} (Symmetric CH_2 str) 1447 cm^{-1} (C-O), 1375 cm^{-1} (-CH_3), 1036 cm^{-1} (R-Cl), 1622 cm^{-1} (-C=O). Results were confirmed that characteristic absorption peaks of pure drug have appeared in the spectra of its physical mixtures without any significant change in their position after successful encapsulation. It indicates absence of chemical interactions between the drug and excipients [Figure 1].

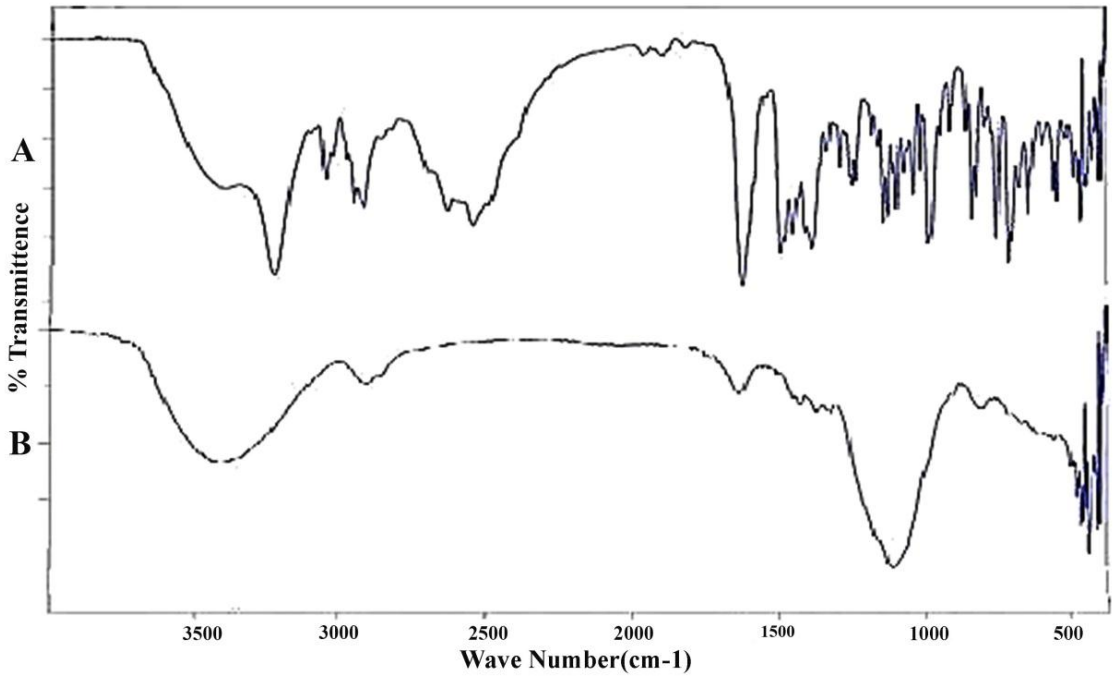

Figure 1. FTIR spectra of LPM with Excipients. A) FTIR spectra of formulation (F2), B) FTIR spectra of pure drug

Selection of vehicle

Solubility of drug in a non-volatile vehicle is an important aspect in liquisolid system. The solubility of drug was determined using solvents (tween 20, tween 80, PEG 200, PEG 400, PEG 600 and PG) and depicted in Table 2. Based on the solubility data, PG was selected as a vehicle for LPM.

Table 2. Solubility of LPM in different solvents

Solvent	Solubility (mg/mL)
Tween 20	71.63±2.12
Tween 80	75.86±2.38
PEG 200	68.12±1.84
PEG 400	70.14±1.92
PEG 600	81. 27±1. 27
PG	149.65±1.38

Results were expressed in mean ± SD

Liquisolid compacts

According Spireas et al,[9] particles with more absorption properties should be used as the carrier material such as starch, lactose and cellulose. High absorption of carrier material is due to the presence of porous surface in the particles. The necessity of coating material is to cover the surface and maintain the flowability.[23] Challa naven et al conducted the binding capacity experiments for carrier materials such as lactose, Avicel pH 102 and dicalcium phosphate. They suggested that Avicel pH 102 possessing much binding capacity. Hence, it was selected as a carrier material and Aerosil 200 as a coat material. Liquisolid tablets of LPM were prepared with different excipients ratio (R) using PG as vehicle (Table 1). The suitable quantities of the carrier and coating material were derived from their liquid load factors. Formulations (F4-F9) with L_f were greater than 0.25 showing poor flowability and compressibility.[24] The angle of repose is a result of internal frictional forces of the particles and it will be higher if the particles are cohesive. The ideal angle of repose values of less than 25, 25-30, 30-40 and greater than 40 indicates excellent, good, passable and very poor respectively.[25] Powder formulations with angles of repose >40° were not acceptable (F4-F9). Formulations F1, F2 and F3 showed 28°, 29°, and 29° respectively. Hence, the formulations F1, F2 and F3 were selected for further studies.

Evaluation of compressed tablets

Tablets should possess the sufficient hardness to withstand breakage during handling and meanwhile, it should also disintegrate after swallowing. Formulations F2 and F3 showed good compressibility with an acceptable hardness 3 kg/cm^2. Formulation F1 showed hardness of 4.5 kg/cm^2 (greater than F2 and F3) and it is due to the presence of more carrier material. Friability was determined (Table 3) and all the formulations were satisfied the official specifications (i.e. <1 %).[22] Drug content of the formulations F1, F2 and F3 were found to be 96.5%, 98.2% and 92.9% respectively. Formulations F1, F2 and F3 were complied with official specifications of USP (i.e. allowable percentage difference for the tablets having the weight of <130 mg is 5% and 130-324 mg is 7.5%).[26] Disintegration time was determined using USP disintegration apparatus and results (Table 3) were found to be 3 min (F1), 2 min (F2) and 3 min (F3). Aerosil also possesses a disintegration property along with SSG.[27] Formulation F2 showed least disintegration time of 2 min and it is due to the combined disintegration property of the Aerosil and SSG. Hence, formulation F2 was selected for further studies.

Table 3. Evaluation of liquisolid tablets of LPM

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	2	0.65	98.2
F3	302 ± 3.11	3.0 ± 0.01	3	0.53	92.9

*Results were expressed in mean ± SD (n=3)

Dissolution improvement

Dissolution studies for liquisolid formulations, pure drug and marketed product were conducted in pH 1.2 HCl dissolution media for 2 h and results were presented in Figure 2.

From the dissolution data, it was observed that 85 % of the drug was released from liquisolid formulation (F2) in 15 min, whereas the marketed product and pure drug showed 35 % and 10 % in 15 min. At the end of 30 min time interval, F2, marketed product and pure drug showed the drug release of >85 %, >60 % and >15 % respectively.

The increased dissolution of liquisolid formulation is mainly due to the presence of solubilised sate of drug in the formulation (molecular dispersion form), which contributes to increased wetting properties thereby enhancing the dissolution rate. It might be expected that F2 can able to show a rapid therapeutic action due to its optimum drug release within a short period of time compared to the marketed drug and pure drug.

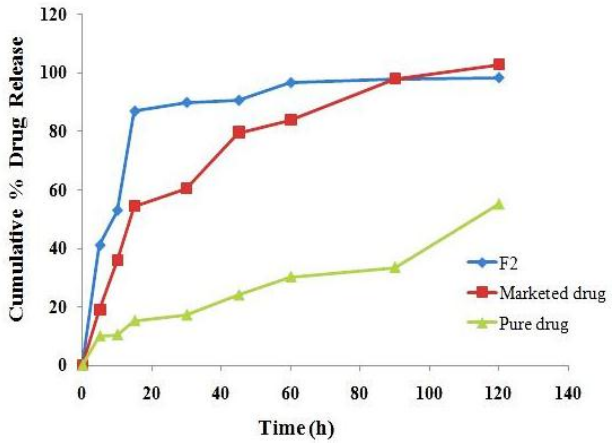

Figure 2. Dissolution profile of F2, Marketed drug and Pure drug

Stability studies

Stability studies were carried out for the selected formulation F2. It was observed from the results that there is no significant changes occurs in the drug content, disintegration time, hardness, friability and *in-vitro* drug release at various sampling intervals of the study (Table 4).

Table 4. Stability studies of liquisolid formulation F2 at 40 ± 2°C & 75 ± 5% RH

Time Intervals	% CDR$^{\$*}$	Hardness (kg/cm^2)*	Disintegration Time (min)	Friability (%)	Drug Content (% w/w)
Initial	98.27 ± 0.9	3.0 ± 0.05	2	0.65	98.2
1 Month	98.15 ± 0.6	3.0 ± 0.40	2	0.64	98.0
2 Month	98.02 ± 0.4	2.92 ± 0.6	1.98	0.62	97.8
3 Month	97.87 ± 0.8	2.91 ± 0.5	1.96	0.60	97.5

*Results were expressed in mean ± SD (n=3), $ % Cumulative Drug Release

Conclusion

Liquisolid technique was found to be a promising approach for improving the dissolution of poorly soluble drugs like LPM. Solubility studies showed the LPM was highly soluble in PG when compared to the other solvents. The dissolution rate of LPM was significantly increased in liquisolid formulation (F2) for a short period of time compared to the marketed product and it might be due to the increased wetting and surface area of the particles. It was concluded from the results that the formulation F2 has. wider scope for future *in vivo* studies.

Ethical Issues

Not applicable

Conflict of Interest

The authors report no conflicts of interest.

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