

PREPARATION AND *IN-VITRO* EVALUATION OF LOPERAMIDE HYDROCHLORIDE SPHERICAL CRYSTALS BY EMULSION SOLVENT DIFFUSION TECHNIQUE

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Received: 30 Jan 2013, Revised and Accepted: 10 Mar 2013

ABSTRACT

The present investigation highlights a significant effect of polymer on improving solubility, dissolution rate and physicochemical properties of loperamide hydrochloride. Spherical crystallization technique with incorporation of polymer is used to improve the bioavailability of poorly water soluble drugs, the flow and direct compressibility of drugs. The objective of this work was to enhance bioavailability of Loperamide Hydrochloride by spherical crystallization technique. Emulsion solvent diffusion technique is used with ethanol-chloroform-water as solvent system. Polyethylene glycol and eudragit were used as hydrophilic and hydrophobic polymers respectively for recrystallization. Pure loperamide and its spherical crystals were characterized by flowability, packability, dissolution rate, FTIR, SEM and XRD. As hausners ratio was less than 1.25 and Carr's index values were less than 25, hence they were found to be free flowing. Among the two polymers eudragit and PEG, PEG with 1:1 proportion was found to be more suitable for increasing dissolution rate of Loperamide Hcl. Thus the prepared spherical crystals with PEG establish excellent solubility and physicochemical properties.

Keywords: Loperamide hydrochloride, Packability, Quasi-emulsion solvent diffusion system, Solubility, Dissolution

INTRODUCTION

The quality of a solid pharmaceutical preparation is influenced by primary micromeritic characteristics such as the shape and size of drug crystals, especially when large amounts of poorly soluble drugs are formulated. To improve the dissolution rate of poorly soluble drugs, fine crystals are preferred over large crystals because they provide a greater surface area. Now days, the most importance is given to enhance the dissolution rate of the poorly soluble drugs, so, it increases the bioavailability of drug. [1]

However, micronization can change drug powder properties such as wettability, compressibility, packability and flowability and thus prevent efficient powder packaging. This technique involves selective formation of agglomerates of crystals which could be easily compounded with other pharmaceutical powders due to their spherical shape [2]. It is a simple process and inexpensive which reduces time and cost by involving faster operation, less machinery, and fewer personnel, with great advances in tableting technology. Using this technology, physicochemical properties of pharmaceutical crystals are dramatically improved for pharmaceutical processing [3].

Spherical crystallization is carried out by different methods such as Spherical agglomeration method, Quasi-emulsion solvent diffusion system (QESDS), Ammonia diffusion system and Neutralization technique. Out of these techniques, the QESDS is most commonly used [4]. Using this method, spherical crystallization can be carried out by using a mixed system of three partially miscible solvents, i.e. good solvent-bridging liquid-poor solvent. When bridging liquid plus good solvent of API are poured into the poor solvent under agitation, quasi-emulsion droplets of bridging liquid or good solvent forms the emulsion droplets in the poor solvent and induces crystallisation of drug followed by drug.

Loperamide hydrochloride (LPH), an anti diarrhoeal agent has poor flow properties and compressibility. It is a white or yellowish white crystalline powder. It has limited aqueous solubility as well as a slower dissolution rate, which is absorbed slowly and erratically after oral administration and thus requires higher dose [5].

In order to overcome the limitations associated with solubility, dissolution, flowability and compressibility, the spherically agglomerated crystals of LPH were prepared in the present investigation. A convenient and cheaper method, QESDS is used for its preparation.

Additionally, hydrophilic polymers (polyethylene glycol) and pore-forming hydrophobic polymer (Eudragit) during crystallization

imparted better solubility, dissolution rate, compressibility and strength.

MATERIALS AND METHODS

Loperamide hydrochloride was obtained as a gift sample from Bajaj Health Care Pvt. Ltd., Mumbai (India). Polyethylene glycol and Eudragit was obtained from Sigma Aldrich Mumbai (India). All other chemicals like ethanol and chloroform were obtained from Loba Chemie, Mumbai.

Preparation of LPH agglomerates by solvent diffusion technique

LPH (2.5 g) was dissolved in the mixture of good solvent ethanol (15 ml) and bridging agent chloroform (5 ml) thermally controlled at 40°C so as to form the saturated solution of the drug. The solution was poured into 80 ml of distilled water (poor solvent) with a stirring rate of 1000 ± 50 rpm using a propeller type of agitator at room temperature. After agitating the system for 10 min, the prepared agglomerates were collected by filtration through Whatman filter paper no. 42 under vacuum. The spherical crystals were washed with distilled water and placed at 45°C for drying in a hot air oven for 24 h and then stored in desiccators [6], [7] [8].

Incorporation of polymer

Eudragit was dissolved along with LPH (1:0.8) in the mixture of ethanol and chloroform. PEG 4000 was first dissolved in distilled water and then with LPH (1:1) in mixture of ethanol and chloroform. The different ratios of drug: Polymers were given in Table 1.

Table 1: Different compositions of drug and polymer

Polymer	Drug: polymer mass ratio
Eudragit	1:0.6
	1:0.8
	1:1
PEG 4000	1:0.8
	1:1
	1:1.2

Evaluation of spherically agglomerated crystals

Solubility Studies

Solubility studies were carried out using deionised water as a solvent. The suspension was treated at room temperature with 100 rpm in an incubator shaker. After 24 h, the samples were withdrawn and filtered. The filtrate was diluted with solvent and analyzed at 237 nm by UV

Visible spectrophotometry. The study was performed in triplicate. The optimized temperature and agitation speed for drug solution and dispersion medium was 25°C and 1000 ± 50 rpm respectively.

Determination of drug contents

Prepared LPH agglomerates equivalent to 100 mg was accurately weighed, crushed, and transferred to a 100 ml standard conical flask. To this, 10 ml of ethanol was added and sonicated for 20 min, volume was made up to mark with 1% SLS (sodium lauryl sulphate) and filtered through a Whatman filter paper. From the resulting filtrate, 1 ml solution was taken and diluted to 50 ml so as to form 20 mg/ml and the absorbance was measured at 237 nm against a blank reagent using a UV visible spectrophotometer. The concentration of the drug present in the formulation was computed from the calibration curve [9].

Determination of fluff density, bulk density and tapped density

0.8gm of powder was placed in 10ml measuring cylinder and poured volume was determined. Measuring cylinder was tapped for 3 times and bulk volume was measured. Measuring cylinder was tapped for 50 times and tapped volume was measured and fluff density, bulk density and tapped density were calculated [10], [11].

Determination of flow properties

The flow rate and angle of repose was determined by the fixed funnel method. 0.8gm of powder was placed in the funnel, which is attached to the burette stand at 2cm above from the bottom of platform. Time required to flow the powder from funnel was measured, and flow rate was calculated [12]. Flowability of LPH and its agglomerated crystals were also determined in terms of Carr's compressibility index, and Hausnar ratio.

Dissolution Studies

Microcrystalline/agglomerates (25 mg) of LPH were placed in muslin in a rotating basket and then placed in 250 ml phosphate buffer and stirred at a speed of 100 rpm with temperature maintained at 37 ± 1°C. Aliquots of 5 ml were withdrawn at appropriate time intervals and an equal volume of water was replaced in the vessel. The drug content was determined spectrophotometrically at 237 nm [13].

Characterization of agglomerated crystals

Surface Morphology by scanning electron microscopy

The surface morphology and shape of spherical crystal containing LPH was investigated using SEM by using scanning electron microscope at suitable magnification.

Melting point determination

The melting points of the spherically agglomerated crystals were determined using the capillary tube method [14].

X-Ray Diffraction

All the selected formulations and pure drug were subjected to X-ray diffraction study. The XRD patterns were recorded on a PW1729, Philips diffractometer (Institute of chemical technology Mumbai.) using Ni-filtered, CuK α radiation, a voltage of 40kV and a 25-mA current. The scanning rate employed was 10 min⁻¹ over the 10 to 300 diffraction angle (2 θ) range.

Infrared Spectroscopy

In order to check any interaction between drug and excipients, the IR spectra of pure drug and excipients [1:1] were carried out using Shimadzu 8400s FT-IR spectrophotometer. The samples were prepared as KBr disks compressed under a pressure of 10 Ton/nm² [15].

RESULTS AND DISCUSSION

Solubility Study

The spherical crystals of LPH showed improved solubility especially in water as indicated in Table 2. PEG crystals (0.476 mg/ml) and eudragit crystals (0.348 mg/ml) showed marked increase in water solubility as

compared to raw LPH (0.221 mg/ml). The presence of a quaternary group in eudragit may be responsible for increase in the solubility of LPH. The agglomerated crystals prepared by incorporating water-soluble polymers can improve solubility. In the present work thus, addition of PEG water-soluble polymer found to increase the solubility of LPH in water as well as in the dissolution medium [16].

Drug Content and production yield

The method used for the preparation of agglomerated crystals was the QESD in which droplets of the solvent formed the quasi emulsion. The continuous phase is a liquid in which the drug solution is immiscible and crystallization occurs inside the droplets because of counter diffusion of solvents through the droplets. The average diameter of the agglomerated crystals increased with increasing content of chloroform in the system due to the enhanced agglomeration of powdery crystals. When the amount of ethanol in the system was increased keeping the amount of chloroform constant, the diffusion rate of ethanol and chloroform from the droplets were enhanced with increasing the content of ethanol in the system. Thus, diameter and recovery of agglomerates decreased with increasing the ethanol content in the system [17]. All agglomerated crystals showed a drug content between 80 to 88.65% and production yield between 75 to 81%.

Micromeritic Studies

Flowability of the spherically agglomerated crystals was studied in terms of angle of repose, Carr's index and Hausnar ratio, bulk density, tapped density, showed in Table 2. LPH have a significantly higher angle of repose in comparison with the spherical agglomerates, which could be due to the irregular shape of the crystals, which hindered in the uniform flow of crystals from the funnel, Results of all parameters it is conclude that agglomerates shows better flow properties than raw crystals. The reason for the excellent flowability of spherical crystals is the significant reduction in the inter particle friction because of the perfect spherical shape and the larger size of the crystals. The Carr's index revealed that the flowability of the LPH was significantly poor than that of the agglomerated crystals. The Hausnar's ratio of the agglomerated crystals was found to be less than 1.25, which also indicates improvement in the flowability of the agglomerated crystals [18].

From the values of all these parameters, it is proved that the agglomerated crystals showed a higher packability than that of raw LPH crystals due to the lower surface and the wider particle size distribution of the spherical crystals.

The spherical agglomerates showed a lower melting point 212-214°C (PEG crystals) and 222-224°C (Eudragit crystals) as compared with the raw material (228-230°C) as shown in Table 2. This decline in melting point of recrystallized samples as compared with raw LPH may be attributed to the variation in crystallinity due to the alteration in the packing arrangement of the molecules in the crystals.

Table 2: Evaluation of LPH and its agglomerated crystals

Evaluation parameters	Raw LPH	PEG crystals	Eudragit crystals
Melting point	228-30 ^o C	212-14 ^o C	222-224 ^o C
Solubility (mg/ml)*	0.221±0.3	0.476±0.5	0.348±0.8
Bulk density g/cc*	0.78 ±0.45	1.02 ±0.76	0.95 ±0.56
Tapped density g/cc*	1.34 ±0.25	1.75 ±0.11	1.62 ±0.43
Bulkiness	1.28±0.65	0.571±0.33	0.471±0.45
Hausnar's ratio *	2.78± 1.33	1.05± 0.92	1.18± 0.53
Carr's	41.79±0.50	24.50±0.45	35.32±0.12
Compressibility Index* (%)			
Angle of repose*	42.34 ^o ±0.45	28.47 ^o ±0.33	32.47 ^o ±0.33

* Each value represent mean S.D. ± (n=3)

Dissolution study

In the dissolution study, PEG agglomerates showed (92.14%) cumulative drug releases in 21 min followed by Eudragit agglomerates (87.16%) as compared with raw LPH (45.14%),

Figure 1. The faster and high dissolution might be due to better wettability of the spherically agglomerated crystals.

Characterization of agglomerated crystals

SEM studies of raw LPH and the prepared agglomerated crystals (**Fig. 2**) showed that the original drug were irregularly pattern as compared with the agglomerated crystals, which were spherical in shape.

The IR spectra (**Fig. 3 and 4**) of drug and spherical crystals showed that no changes occurred in the chemical nature and did not present a great fingerprint difference.

XRD analysis of the pure drug and selected batches were performed. It is generally stated that if three consecutive Relative intensity percentage values in XRD pattern decreases it can be confirmed as decrease in crystallinity had occurred in samples. XRD Patterns of LPH and selected formulations were given in **Fig 5**. XRD pattern of LPH showed numerous sharp, narrow and intense peaks, claiming its high crystallinity. The patterns of formulations showed no/little peaks indicating its amorphous nature. These observations from comparison of XRD pattern can be treated as confirmation tool for reduction in crystallinity and phase transition (from crystalline to amorphous form) had occurred in the samples.

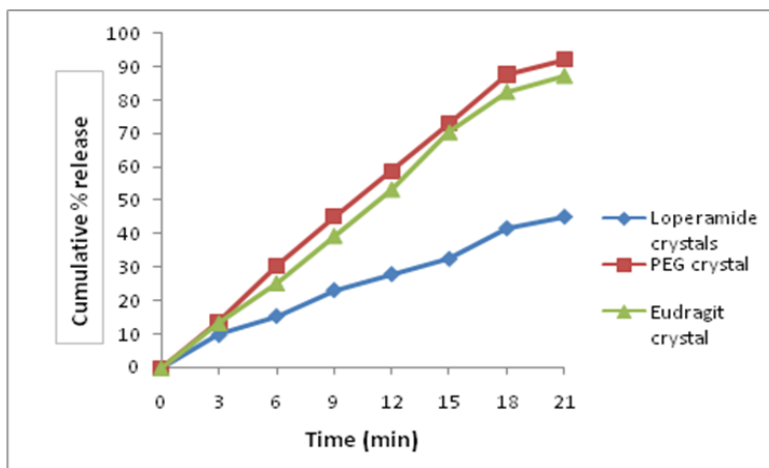


Fig. 1: In Vitro Drug Release Profile

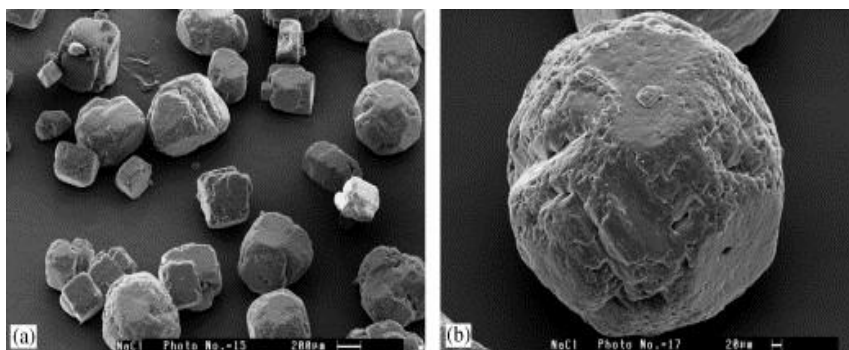


Fig. 2: a) SEM of LPH b) SEM of LPH Spherical Crystals of PEG

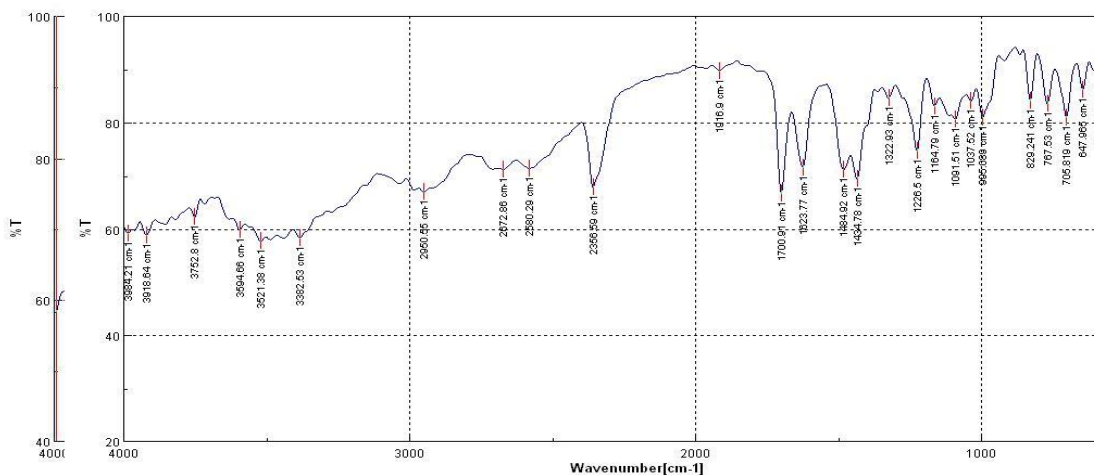


Fig. 3: IR Spectra of raw LPH

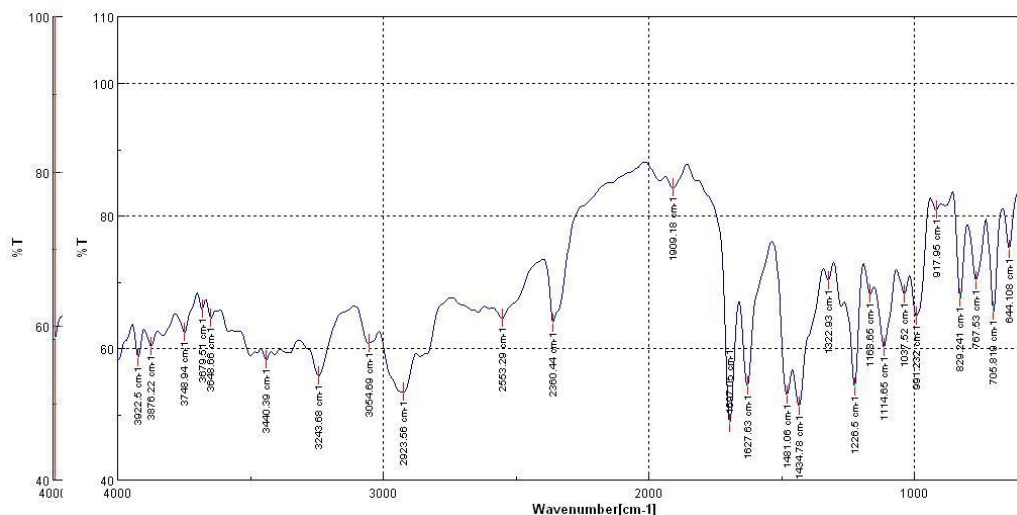


Fig. 4: IR Spectra of spherical crystals of LPH

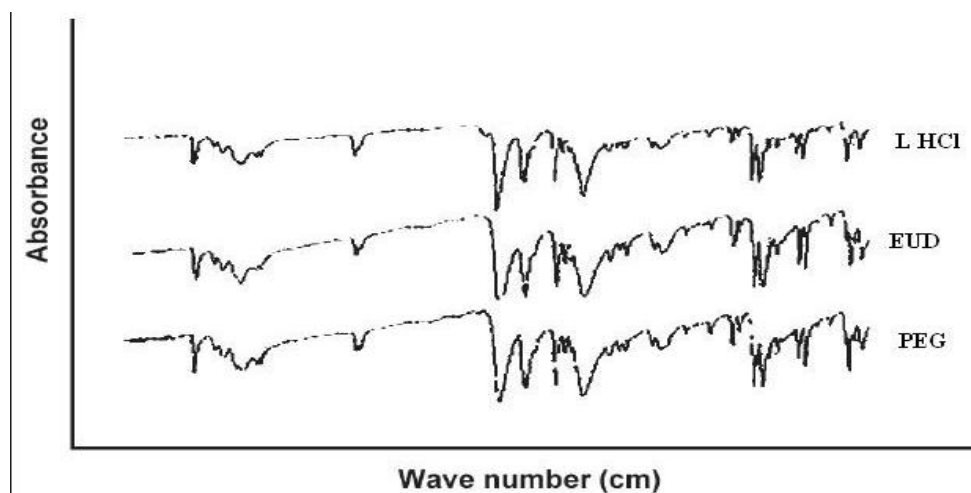


Fig. 5: X-ray diffraction pattern of LPH, EUD and PEG Crystals

CONCLUSION

From the above observations, we can conclude that agglomerated crystals of LPH with different hydrophilic and hydrophobic polymers prepared by the Quasi Emulsion Solvent Diffusion technique showed an improvement in the solubility, dissolution rate, packability and flowability. PEG was found to be a better polymer in dissolution and bioavailability enhancement of LPH from agglomerates.

REFERENCES

- Gupta M.M., Patel M. G., Patel N. S., Madhulika K. Enhancement of dissolution rate of Ibuprofen by Preparing solid dispersion using different methods. *Int J Pharm Pharm sci* 2011; 03: 204-206.
- Kawashima Y, Yang L, Nito M, Takenaka H. Direct agglomeration of sodium theophylline crystals produced by salting out in the liquid. *Chem.Pharm Bull* 1982; 30:1837-43.
- Morshima K, Kawashima Y, Takeuchi H, Niwa T, Hino T. Tableting properties of Bucillamine agglomerates prepared by the spherical crystallization technique. *Int Jr Pharm* 1994; 105:11-8.
- Hector GP, Jorge B and Carlo A. Preparation of Norfloxacin spherical agglomerates using the ammonia diffusion system. *Jr Pharm Sci* 1998; 87:519-23.
- United State Pharmacopoeia. Vol. II. Rockville MD: The United States Pharmacopoeia Conventions; 2000, 984-985.
- Jbilou M, Ettabia A, Guyot-Hermann AM, Guyot JS. Ibuprofen agglomeration prepared by phase separation. *Drug Dev Ind Pharm* 1990; 25:297-305.
- Kawashima Y, Niwa T, Handa T, Takeuchi H, Iwamoto T. Preparation of controlled release microspheres of Ibuprofen with acrylic polymers by a novel quasi-emulsion solvent diffusion method. *J Pharm Sci* 1989; 78:68-72.
- Najmuddin M., Tousif Khan, Mohsin A.A., Shelar S., Patel V. Enhancement of dissolution rate of ketoconazole by solid dispersion technique. *Int J Pharm Pharm Sci* 2010; 02: 132-136.
- Ravichandran V, Sivanand V, Raguraman S, Velrajan G, Balaji S. Micro encapsulation of Nimeslide for sustain release. *Indian Pharmacist* 2001:111-4.
- Martin A., Bustamante P. and Chum A.H.C. *Micromeritics in Physical Pharmacy*. Waverly International, Maryland. 4th ed 1995; 492-522.
- Gennaro A.R. *Remington's Pharmaceutical Science*. Mack Publishing Company, Pennsylvania. 18th ed 1990; 1615-1645.
- John S., Aulton ME. In *Pharmaceutics: The Science of Dosage Form Design*, International Student Edition, ELBS. Edinburgh: Churchill Livingstone 2002;205.
- Sharma, Y. R. *Elementary Organic Spectroscopy: Principles and Chemical Application* 81.

14. Kotteke M.K., Rudnic E.M. In Banker: Tablet Dosage forms. New York 4th ed 2002:291-333.
15. Kawashima Y, Aoki S, Takenaka H. Spherical agglomeration of Aminophylline crystals during reaction in liquid by the spherical crystallization. Chem Pharm Bull 1982;30:1900-2.
16. Labhassetwar V, Deshmukh SV, Dorle AK. Studies on some crystalline forms of Ibuprofen. Drug Dev Ind Pharm 1993;19:631-41.
17. Sano VP, Kuriki T, Handa T, Takeuchi H, Kawashima Y. Particle design of Tolbutamide in the presence of soluble polymers or surfactant by the spherical crystallization technique: Improvement of dissolution rate. Jr Pharm Sci 1987;76:471-4.
18. Kawashima Y, Ima M, Takeuchi H, Yamamoto H, Kamiya K, Hino T. Improved flowability and compactibility of spherically agglomerated crystals of ascorbic acid for direct tableting designed by spherical crystallization process. Powder Technol 2003;130 :283-9.