REVIEW

Comparative evaluation of various solubility enhancement strategies for furosemide

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Abstract: Drugs with good solubility exhibit good oral absorption, and subsequently good bioavailability. Thus, most exigent phase of drug development practice particularly for oral dosage forms is the enhancement of drug solubility. This review describes various traditional and novel methodologies proposed for the solubility enhancement of furosemide. For furosemide, solubility and permeability are crucial rate limiting factors to achieve its desired level in systemic circulation for pharmacological response. Thus, problematic solubility of furosemide is one of the main challenges for dosage form developing researchers**.** Various procedures, illustrated in this review, have been successfully employed to improve the furosemide solubility; however successful improvement essentially depends on the assortment of technique. It is concluded from the results that dissolution rate of drug increases by increasing the quantity of solubility enhancer. Dissolution rate also depends upon the type of enhancer and dissolution medium. In order to achieve relatively enhanced percentage drug release after 30 min (DP_{30}), complexation by solvent evaporation using β-cyclodextrin is the best method. Solid dispersion is found the best if polyethylene glycol is used as enhancer along with microcrystalline cellulose as hydrophilic adsorbent. All the approaches narrated in this article possess good perceptions for additional research i.e. *in-vivo* studies should be carried out focusing on delivery system development.

Keywords: Furosemide, solubility enhancement, polymers, dissolution.

INTRODUCTION

Drug solubility may be defined as the maximum amount of the drug solute that is dissolved in a saturated solution under specific conditions of temperature, pH and pressure. It is expressed in terms of percentage, volume fraction, molarity, molality, mole fraction and parts. Dissolution of a drug is a process of transfer of its particles (ions or molecules) to the solution in which it is placed (Aggarwal *et al.,* 2010). According to the solubility criteria, parts of solvent required for one part of solute are given in the brackets in front of each solubility category: very soluble (<1), freely soluble (1-10), soluble (10-30), sparingly soluble (30-100), slightly soluble (100-1000), very slightly soluble (1000-10,000), and insoluble (>10,000) (USP30-NF25, 2007). The solubility depends upon the physical properties (particle size, polarity, pKa, and polymorphs) of solids, and the nature, composition, temperature and pressure of solvent system (Karanth *et al*., 2006; Moneghini *et al*., 2005). The solubilization process needs the intrusion of inter-ionic or intermolecular bonds in solute (Biswal *et al.,* 2009), partitioning of solvent molecules to make available the space in solvent for solute, and the contact between the solvent and solute molecule or ion (Karanth *et al*., 2006).

Therapeutic effectiveness of a drug directly relates to its bioavailability which in turn depends upon the solubility of drug. Drugs having both, high solubility and permeability, comprise only 8% of new drug candidates. Unfortunately, more than 67% of total drugs listed in United States Pharmacopeia come under the umbrella of poorly water soluble drugs (Ahire *et al*., 2010). During drug development, about 40% of them fail due to the low solubility and thus poor pharmacokinetic profiles (Van de Waterbeemd and Gifford, 2003). Solubility is, therefore, one of the crucial factors to attain desired concentration of drug in systemic circulation and ultimately to show pharmacological response. Conclusively, therapeutic efficacy of a drug depends upon the solubility and bioavailability of drug. Poor water solubility depends upon two important parameters; (i) high lipophilicity and (ii) strong intermolecular forces which results in slow solubilization (Anette *et al*., 2003).

Biopharmaceutical Classification System (BCS) was first time proposed by Amidon *et al*. (1995). According to BCS, drugs are divided into four classes on the basis of solubility and permeability. These classes are as; class I drugs: High solubility-high permeability, class II drugs: Low solubility-high permeability, class III drugs: High solubility-low permeability and class IV drugs: Low solubility-low permeability (Amidon *et al*., 1995).

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Furosemide is a low solubility drug which belongs to BCS class IV (Amidon *et al*., 1995; Fasinu *et al*., 2011; Smolen and Weigand, 1973; Pang, 2003). Thus, the rate and extent of gastrointestinal absorption of furosemide is controlled by its solubility and permeability (Murray *et al*., 1988). It shows little bioavailability possibly due to its hydrophobic nature. The increase in furosemide solubility is therefore, a valuable objective for enhancing its therapeutic efficacy. Furosemide is a loop diuretic which is extensively used in different conditions of edema. Its chemical formula is 4-chloro-2-(2-furylmethylmino)-5-sulfamoyl-benzoic acid. Due to acidic nature (pKa 3.9), it is mostly absorbed from stomach and upper small intestine (Karkhile *et al*., 2010).

A drug should necessarily be present in soluble form before absorption. A number of techniques are employed to improve solubility of low solubility drugs. Super-saturation is, in fact, a reality; solubility enhancing techniques do not augment the solubility of insoluble drugs. Rather, these approaches present the drug in a form which is optimal to its solubility. These techniques include solid dispersion, solvent disposition, co-solvents, salt formation, pH control, micronization, co-grinding, use of surfactants, use of precipitation inhibitors, solid solution, selective adsorption on insoluble carriers and complexation (Karkhile *et al*., 2010; Vemula *et al*., 2010; Gershkovich and Hoffman, 2005; Deepika *et al*., 2008).

In solid dispersion, solvent free solid dispersion are prepared for solubility enhancement where dispersion of drug takes place in a highly water soluble matrix whereby the drug is dispersed in a hydrophilic matrix and solid solution or eutectic mixture is formed (Craig, 2002; Sekiguchi and Obi, 1961; Hulsmann *et al*., 2000). In solid dispersion technique, drug and carrier is dissolved in a volatile solvent. The solvent is evaporated at reduced pressure or by freeze drying (solid dispersion via solvent evaporation) and the precipitate of drug in carrier is left behind (Jain *et al*., 2010). Solid dispersion can also be prepared by kneading method (Ahire *et al*., 2010). Kneading method involves the trituration of drug with carrier in a small volume of solvent to produce a thick paste, which is kneaded for 30 min followed by drying. After pulverization, the dried mass is transferred through suitable sieve and the product is packed in air-tight container (Ahire *et al*., 2010).

In complexation, the hydrophobic drugs are reacted with substances like cyclodextrins to enhance their solubility (Jain *et al*., 2010; Corrigan and Stanly, 1982) through the formation of bonds like non-covalent bonds (Uekama *et al*., 1982). Some other complexating agents are caffeine, urea, polyethylene glycol, and N-methylglucamide (Jain *et al*., 2010; Corrigan and Stanly, 1982).

For the preparation of inclusion complexes via co-precipitation method, drug and carrier are dissolved in a suitable solvent by prolonged stirring, and then the mixture is placed at 0°C. It causes the microcrystalline precipitation followed by its filtration, washing and drying (Sapkal *et al*., 2007).

In liquisolids technique, the drug (in the form of liquid, solution or suspension) is blended with carrier and coating material to achieve a dry-looking, non-adherent, free flowing and readily compactable powder to improve dissolution rate (Akinlade *et al*., 2010; Spireas *et al*., 1999; Javadzadeh *et al*., 2005; Javadzadeh *et al*., 2007; Tiong and Elkordy, 2009; Nokhodchi *et al*., 2005). As dissolution is usually the rate determining phase in gastrointestinal absorption of a drug, significant enhancement in wetting characteristics and exposed surface area of drug molecules accessible for dissolution from semi-solid products may predominantly be supposed to exhibit increased drug release features and eventually improved oral bioavailability of drug (Gould and Scott, 2005).

Emulsification is also used for solubility enhancement. In self micro-emulsifying system, mixture of oil surfactant and hydrophilic co-surfactant is present. When this mixture encounters with gastrointestinal motility, oil-in-water type microemulsion is produced (Zvonar *et al*., 2010; Shah *et al*., 1994). Classification of carriers enhancing dissolution of drugs is mentioned in table 1 (Saleh and Daabis, 1974; Saharan *et al*., 2009; Rasool *et al*., 2002).

Finally, the efficiency of each technique is evaluated by comparing the products with that obtained by physical mixing. A physical mixture (reference product) is obtained through mixing the pulverized drug and carrier in a specific ratio using a mixer and then the mixture is sieved. A mixing time of 10-20 min is enough; however mixing should be continued till the formation of a homogeneous final product (Loftsson and Duchene, 2007; Badwana *et al*., 1982).

All the above-mentioned techniques have their own limitations, for example, decreasing particle size decreases wetting ability and flow properties which can be solved by the process of solid dispersion. Due to the difference in chemical structures and other properties, all drugs cannot be changed to salt form to improve dissolution (Ahire *et al*., 2010).

Hence, many studies are being carried out for increasing the dissolution rate of hydrophobic furosemide, for enhancing efficacy and concurrently reducing its dose and side effects (Patel *et al*., 2008; Chauling *et al*., 2009; Patel *et al*., 2010; Patel *et al*., 2005; Ozdemir and Ordu, 1998; Chauling *et al*., 2008; Shin *et al*., 1998; Patel *et al*., 2010b; Vlachou and Papaioannou, 2003; Akbuga *et al*., 1988; Shin and Kim, 2003; Perioli *et al*., 2011; Sanghvi *et al*., 2007). In this article, previous studies involving solubility enhancement strategies for furosemide are

compared to explore the best one. The drug to polymer ratio, which gave highest percentage drug release after 30 min (DP_{30}) from each study was approximated from the given dissolution curves and in some cases, from the tabular data presented in previous publications.

Literature search methodology

A comprehensive literature (in English only) search was conducted using electronic databases: Medline (1966-2011) and EMBASE (1980-2011). For a simple search, initially "solubility enhancement" and "furosemide" were separately used as search terms and then an advanced search was made by combining all search fields in abstract, key words, or title, To make certain a comprehensive review, investigation of literature was supplemented by probing the reference lists of the selected papers created from the original investigations. The authors selected the potentially appropriate papers identified by the electronic searches. The published literature eligible for inclusion were the *in vitro* studies presented in the English language. All the literature selected was confirmed for duplications, which if observed were excluded.

Statistics

In all cases, analysis of the data was achieved by applying one-way ANOVA with a probability of $p<0.05$ set as statistically significant.

DISSOLUTION DATA ANALYSIS

Physical mixtures

Many previous studies elaborate the preparation of physical mixtures of furosemide using various solubility enhancement materials (table 1) in different drug to polymer ratios like 1: 1, 1: 2 and 1: 3 (Karkhile *et al*., 2010; Patel *et al*., 2008; Chauling *et al*., 2009; Patel *et al*., 2010; Patel *et al*., 2005; Ozdemir and Ordu, 1998; Chauling *et al*., 2008; Shin *et al*., 1998; Patel *et al*., 2010b; Vlachou and Papaioannou, 2003; Akbuga *et al*., 1988; Shin and Kim, 2003; Perioli *et al*., 2011; Sanghvi *et al*., 2007). Dissolution studies of all products were conducted in various media (table 2). The analysis of dissolution curves proposed by Vlachou and Papaioannou have indicated that maximum amount of drug release in 30 min was 81% (Vlachou and Papaioannou, 2003), where hydroxylpropyl β-cyclodextrin was employed to enhance dissolution rate of furosemide in a drug to polymer ratio of 1: 4.5 using water as dissolution medium. Cyclodextrins, the cyclic oligosaccharides having hydrophilic surface and lipophilic cavity of a cone like structure, possess excellent features of inclusion complex formation to enhance water solubility of hydrophobic drugs (Sanghvi *et al*., 2007). Due to the presence of lipophilic cavity, cyclodextrins are unique in nature for having capability to bind with lipophilic drugs in a host-guest fashion probably via van der Walls force (Shargel *et al*., 2005). In a study conducted by Patel *et al*., the observed DP_{30} was 21% in which hydroxylpropyl β-cyclodextrin was employed to enhance dissolution rate of furosemide in drug to polymer ratio of 1: 5.5 and the dissolution medium was 0.1 N HCl solution (Patel *et al*., 2010b). This release rate was lower compared to that of elaborated and hydroxylpropyl β-cyclodextrin was used in both cases (Vlachou and Papaioannou, 2003). This difference in the rate of drug release could be attributed to the different dissolution media. Predominantly, fast

Table 1: Classification of carriers enhancing dissolution of drugs (Saharan *et al*., 2009)

Category	Examples
Polymers	Polyvinylpyrrolidone, Polyvinyl alcohol, Hydroxypropyl methylcellulose, Hydroxypropyl cellulose, (Eudragit®S100 sodium salts and Eudragit® L100 sodium salt, Poly (2-hydroxyethylmethacrylate), Methacrylic copolymers, Polyethylene glycols
Super-disintegrants	Sodium starch glycolate, Croscarmellose sodium, Cross-linked polyvinylpyrrolidone, Cross-linked alginic acid, Calcium silicate
Cyclodextrins	β-Cyclodextrins, Hydroxypropyl-β-cyclodextrins
Carbohydrates	Lactose, Soluble starch, Sorbitol, Mannitol, β-(1-4)-2-amino-2-deoxy-D-glucose (Chitosan), Maltose, Galactose, Xylitol, Galactomannan, British gum, Amylodextrin
Surfactants	Poloxamers (Lutrol® F 127, Lutrol® F 68), Polyglycolized glyceride (Labrasol), Polyoxyethylene sorbitan monoesters (Tweens), Sorbitan esters (Spans), Polyoxyethylene stearates, Poly (beta-benzyl-L-aspartate) -b- poly (ethylene oxide), Poly (caprolactone) -b- poly (ethylene oxide)
Hydrotropes	Urea, Nicotinamide, Sodium benzoate, Sodium salicylate, Sodium acetate, Sodium-o-hydroxy benzoate, Sodium-p-hydroxy benzoate, Sodium citrate
Polyglycolized glycerides	Gelucire 44/14, Gelucire 50/13, Gelucire 62/05
Acids	Citric acid, Succinic acid, Phosphoric acid
Dendrimers	Starburst® polyamidoamine (PAMAM)
Miscellaneous	Microcrystalline cellulose, Dicalcium phosphate, Silica gel, Sodium chloride, Skimmed milk

dissolution of furosemide in water as compared to that of acidic medium (0.1 N HCl) can be attributed to acidic nature of drug (pKa=3.9): acidic drugs swiftly dissociate and get dissolved in a medium of high pH compared to that in basic and neutral media (Shargel *et al*., 2005; Oberoi *et al*., 2005). This could be the reason that most of the dissolution studies of furosemide involve the use of 0.1 N HCl as dissolution medium to simulate gastric conditions. The studies in which dissolution medium is gastric simulated fluid i.e. 0.1 N HCl, are also compared. Physical mixtures of polyethylene glycol 6000 and microcrystalline cellulose combination, polyvinyl pyrrolidone (drug to polymer ratio 1: 20), polyethylene glycol 6000 (drug to polymer ratio 1: 6), crospovidone (drug to polymer ratio 1: 2 using kneading method) and sodium starch glycolate (drug to polymer ratio 1: 2) gave 100, 93, 84.34, 76.5 and 76% drug release after 30 min, respectively using 0.1 N HCl solution as dissolution medium. The increase in furosemide dissolution, in case of all these physical mixtures, could be attributed to many factors like lack of crystallinity (amorphization), augmented dispersibility and wettability, reduction in particle size, and increase in the exposed surface area (Lee *et al*., 2003). Physical mixtures of β-cyclodextrin (drug to polymer ratio 1: 4.5) and mobile crystalline material (MCM, drug to polymer ratio 1: 0.72) gave 100% and 81% drug release after 30 min, respectively where the dissolution medium was 0.1 N HCl solutions (Patel *et al*., 2010; Perioli *et al*., 2011). In another study, 71% of drug release from physical mixture of furosemide and mobile crystalline material (MCM) was observed (Ambrogi *et al*., 2011). Here the drug was included in the pores of MCM and hence was released easily by-passing the phase of crystalline lattice disruption, a process that needs high energy for dissolution of the drug. MCM is a mesoporous carrier containing several parallel channels. Due to the presence of many hydroxyl groups on its surface, MCM undergoes readily hydrogen bonding with suitable molecules (Ho *et al*., 2011). MCM is considered as an excellent carrier for hydrophobic drugs due to its many versatile features like large exposed surface area, confinement of drug molecules in the narrow area that prevents re-crystallization of drug, presence of channels for assisting the diffusion of drug, and easy breakage of bonds (present between drug and carrier) on contacting with water (Patel *et al*., 2010, Sliwinska-Bartkowiak *et al*., 2001). It is also evident from table 3 when same drug to enhancer ratio (1: 2) and same dissolution media were used, the solubility enhancers were in the following order depending upon their DP_{30}: β-cyclodextrin (DP_{30}=52%) > crospovidone (DP_{30}=26%) > sodium starch glycolate (DP_{30}=25%) > D-a-tocopheryl polyethylene glycol 1000 succinate (TPGS, DP_{30}=35%) as mentioned above due to the varying nature and chemistry of enhancers. TPGS, a hydrophilic ester that is derived from natural vitamin E and polyethylene glycol 1000, has been elaborated as an excellent absorption enhancer. It possesses both hydrophilic and lipophilic parts in its structure which constitutes it the surfactant properties (Sokol *et al*., 1993). The increase in furosemide solubility by employing TPGS could be attributed to its emulsifying role (Traber *et al*., 1986, Wu *et al*., 1996). In various studies, the researchers have also used very high amount of solubility enhancers. For example, Karkhile *et al*. used polyethylene glycol 6000 in 1 : 6 and its DP_{30} value was 24.79% (Karkhile *et al*., 2010). Patel *et al*., used polyethylene glycol 6000 in 1: 10 and its DP_{30} values was 26% (Patel *et al*., 2008). Above all, Akbuga *et al*., used polyvinyl pyrrolidone in 1: 20 and the observed DP_{30} value was 38%. But DP_{30} values for hydroxylpropyl β-cyclodextrin in 1: 4.5 was highest (81%) (Akbuga *et al*., 1988). This indicates that hydroxylpropyl β-cyclodextrin is the best suitable candidate to enhance the dissolution rate of furosemide due to the presence of hydroxyl groups that make it more hydrophilic (Qian *et al*., 2008). The DP_{30} values for the physical mixtures of furosemide with urea and hydroxypropylmethylcellulose E50LV were 7% and 22%, respectively. The higher solubility enhancement feature of hydroxypropylmethylcellulose E50LV could be due to its amorphous nature compared to the crystalline urea (Raval *et al*., 2010).

Solid dispersions

Table 3 shows that solid dispersions are prepared by using different enhancers in different ratios (Gershkovich and Hoffman, 2005; Sekiguchi and Obi, 1961; Uekama *et al*., 1982; Deepika *et al*., 2008; Nokhodchi *et al*., 2005; Akinlade *et al*., 2010; Javadzadeh *et al*., 2005; Nokhodchi *et al*., 2005). Using polyethylene glycol 6000: microcrystalline cellulose (MCC, 16: 25), Patel *et al*. exhibited highest value of DP_{30} (100%) as compared to that of Patel *et al*. (68.2%) due to the presence of microcrystalline cellulose as hydrophilic adsorbent in addition to polyethylene glycol 6000 (Patel *et al*., 2010; Patel *et al*., 2008). This is due to the presence of hydroxyl groups in microcrystalline cellulose (Gao *et al*., 2007). Another reason could be the inclusion of drug in the pores of MCM and thus easily bypassing the phase of crystalline lattice disruption, which is a high-energy process in the dissolution of a drug (Gao *et al*., 2006). Mechanism of increased dissolution rate by solid dispersion involves the (i) reduction in particle size (Muhammed *et al*., 2007), (ii) solublization effect (use of carriers) (Bilensoy *et al*., 2007), (iii) increased wettability and dispersibility by carriers (Luppi *et al*., 2005) and (iv) formation of metastable dispersion with reduced lattice energy for faster dissolution (Maestrelli *et al*., 2006). Moreover, DP_{30} values for PEG 6000 and PVP K30 were 68.2% and 65.1%, respectively in the same conditions of dissolution testing (Teresa *et al*., 2002, Franco *et al*., 2001). Higher increase in furosemide solubility by PEG 6000 could be attributed to the increased wettability resulting in the enhanced solubility as supported by phase-solubility study (using 10% polymer concentration,

furosemide solubility was increased by 27-times and 23-times for PEG 6000 and PVP K30, respectively) (Patel *et al*., 2008). Chaulang *et al*. (Chauling *et al*., 2008) and Shin *et al*. (Shin *et al*., 1998) prepared solid dispersion by kneading and co-precipitation method, respectively using crospovidone in the same drug to enhancer ratio (1: 2), however DP_{30} value was greater for former (26%) than that of the later (5.6%). It can be attributed to the fact that both solubilization and trituration take place during kneading method, which exerts a synergistic effect (Saleh and Daabis, 1974).

In physical mixture and solid dispersion, there is no complexation of *β*-cyclodextrin in the solid state, but it forms *in situ* complexes in dissolution media (Rasheed *et al*., 2008). Solid dispersions of different enhancers show higher dissolution than the corresponding physical mixtures. Because in making solid dispersion, kneading method is efficient due to solubilization and trituration, and crystallinity is also decreased by solid dispersion (Londhe and Nagarsenker, 1999). For example, solid dispersion of furosemide with crospovidone by kneading method showed higher value of DP_{30} (76.5%) than that of the physical mixture (Chauling *et al*., 2008). Preioli *et al*. used hydrotalcite like compounds for dissolution enhancement and its DP_{30} value was 50% at 3.0pH (Patel *et al*., 2005). A comparative dissolution enhancement study for solid dispersions of furosemide crystals prepared using urea and hydroxypropylmethylcellulose E50LV has also been carried out and the calculated values of DP30 for both carriers were 25% and 55%, respectively. The higher solubility enhancement feature of hydroxypropylmethylcellulose E50LV could be due to its less crystallinity as compared to that of urea which is one of the very crystalline substances (Raval *et al*., 2010).

Complexation

In case of inclusion complexation, drug molecules are included inside the enhancer, crystallinity is decreased and hence the drug gets released easily by-passing the phase of crystalline lattice disruption. In table 4, studies conducted by Ozdemir and Ordu, Patel *et al*., and Patel *et al*. are compared in which *β*-cyclodextrin is employed as dissolution enhancer in ratio of 1: 1, 1: 2 and 1: 4.5 with DP_{30} values as 42.5, 93 and 100%, respectively (Ozdemir and Ordu, 1998; Patel *et al*., 2010; Patel *et al*., 2005); It is evident that by increasing the ratio of *β*-cyclodextrin, dissolution rate of furosemide is increased. But after adding excess amount of *β*-cyclodextrin, dissolution may decrease due to the little amount of drug available for dissolution medium to be dissolved (Franco *et al*., 2001; Loftsson *et al*., 2007). Chaulang *et al*. (Chauling *et al*.,

Table 2: Percentage of drug released from physical mixture of furosemide after 30 min

	Material Used	Drug to Enhancer (s) Ratio	DP_{30}	Dissolution Medium	Ref.
1	Polyethylene glycol 6000	1: 6	24.79	0.1 N HCl Solution	Karkhile *et al*., 2010
2	Polyethylene glycol 6000	1: 10	26	Demineralised water containing 0.25% [w/v] of sodium lauryl sulfate	(Patel *et al*., 2008)
3	Polyvinylpyrrolidone K30	1:10	21	Demineralised water containing 0.25% [w/v] of sodium lauryl sulfate	(Patel *et al*., 2008)
4	Sodium Starch Glycolate	1: 2	25	0.1 N HCl Solution	Chauling *et al*., 2009
5	β-cyclodextrin	1: 4.5	10	0.1 N HCl solution	Patel *et al*., 2010
6	β-cyclodextrin	1 : 2	52	Phosphate Buffer (pH=5.8)	Patel *et al*., 2005
7	β-cyclodextrin	1: 1	32.5	0.1 N HCl solution	Ozdemir and Ordu, 1998
8	Crospovidone (Kneading method)	1: 2	26	0.1 N HCl Solution	Chauling *et al*., 2008
9	Crospovidone (co precipitation)	1: 2	5.6	0.1 N HCl solution	Shin *et al*., 1998
10	Hydroxyl propyl β-cyclodextrin	1: 5.5	21	0.1 N HCl Solution	Patel *et al*., 2010b
11	Hydroxyl propyl β-cyclodextrin	1: 4.5	81	Distilled Water	Vlachou and Papaioannou, 2003
12	Polyvinylpyrrolidone	1: 20	38	0.1 N HCl Solution	Akbuga *et al*., 1988
13	D-a-tocopheryl polyethylene glycol 1000 succinate	1: 2	35	0.1 N HCl solution	Shin and Kim, 2003
14	Mobile Crystalline Material	--	71	N HCl Solution	Ambrogi *et al*., 2011
15	Hydrotalcite like compound	2: 1	50	pH = 3.0	Perioli *et al*., 2011
16	Urea	1:5	7	pH = 3.0	Jain *et al*., 2010
17	Hydroxypropyl-Methylcellulose E50LV	1:2	22	pH = 3.0	Jain *et al*., 2010

2008) used sodium starch glycolate (1: 2) and 0.1 N HCl solution as enhancer and dissolution medium, respectively and its DP_{30} value was 76%. Akbuga *et al*. employed polyvinylpyrrolidone (1: 20) and 0.1 N HCl solution as complexating agent and dissolution medium, respectively and its DP_{30} value was 93% (Akbuga *et al*., 1988). Shin and Kim (Shin and Kim, 2003) employed D-α-tocopheryl polyethylene glycol 1000 succinate and 0.1 N HCl solution as enhancer and dissolution medium, respectively and its observed DP_{30} value was 47.5%.

As shown in table 4, Patel *et al*. and Vlachou *et al*. used *β*-cyclodextrin and hydroxylpropyl *β*-cyclodextrin, respectively in the same ratio (1: 4.5). The observed DP_{30} values was 100% for the Patel *et al*. which was significantly ($p<0.05$) greater than the DP_{30} of Vlachou *et al*. (Patel *et al*., 2010; Vlachou and Papaioannou, 2003). The reason is that when the degree of substitution in *β*-cyclodextrin and thus complexating capacity is increased, consequently solubility and dissolution rate is increased. But in case of very bulky substitution, the complexating capacity decreases due to the steric hindrance effect of the bulky substituent (Challa *et al*., 2005). Hydroxylpropyl *β*-cyclodextrin was employed in a ratio of 1: 4.5 by Vlachou *et al*. and the observed DP_{30} value was 96% whereas a ratio of 1: 5.5 employed by Patel *et al*. gave 100% as value of DP_{30} (Vlachou and Papaioannou, 2003; Patel *et al*., 2010b). This shows that by increasing the quantity of solubility enhancer, DP_{30} value is increased. Ambrogi *et al*. employed MCM as complexating agent (1: 0.72) and its DP_{30} value was 81% in 0.1 N HCl solution (Ambrogi *et al*., 2011).

Liquisolid technique

In table 5, liquisolid techniques for dissolution enhancement are compared using 0.1 N HCl solution as dissolution medium (Burra and Galipelly, 2010) in which the combination of avicel PH 102: aerosil 200 (10: 1) showed the burst release effect as evident from very high value of DP_{30} (98.35%) which could be probably due to the increased wetting property and surface area (Burra and Galipelly, 2010), as compared to synperonic® PE/L 81 (polyoxyethylene-polyoxypropylene-polyoxyethylene block copolymer, surfactant) exhibiting a value of DP_{30} = 54%. Fast dissolution from synperonic® PE/L 81 based liquisolid formulation may be due to the excellent solubility of furosemide in synperonic® PE/L 81 (Javadzadeh *et al*., 2007), thus more furosemide (dissolved in synperonic® PE/L 81) absorbs on coating substance which causes an increase in the exposed surface area of drug to the drug resulting in higher dissolution rate of hydrodynamic layer in the microenvironment surrounding the drug particles (Spireas and Sadu, 1998). In addition, some drug particles, not exposed to dissolution medium, mix with the non-ionic synperonic® PE/L 81 resulting in a decrease in interfacial tension between furosemide crystals and dissolution medium and thus increase in wettability. It causes an increase in the furosemide solubility (Tayel *et al*., 2008).

Emulsification technique

Microemulsion exhibits no burst release of furosemide when chitosan (deacetylated chitin) is employed as wall material (table 6); however its dissolution rate was greater than that of pure furosemide crystals. In this study, DP_{30} value was found to be 24% in aqueous solution pH 3.0 as

Table 3: Percentage of drug released from furosemide solid dispersion after 30 min

	Material Used	Drug to Enhancer Ratio	Drug Dissolved (%) After 30 min	Dissolution Medium	Ref.
1	Polyethylene glycol 6000 (Melting method)	1: 6	84.34	0.1 N HCl Solution	Amidon *et al*., 1995
2	Polyethylene glycol 6000 (Solvent evaporation)	1: 10	68.2	Demineralised water containing 0.25% [w/v] of sodium lauryl sulfate solution	Nokhodchi *et al*., 2005
3	Polyvinylpyrrolidone K30	1:10	65.1	Demineralised water containing 0.25% [w/v] of sodium lauryl sulfate	Patel *et al*., 2008
4	Polyethylene glycol 6000: Micro crystalline cellulose (16: 25)	--	100	N HCl Solution	Ozdemir and Ordu, 1998
5	Sodium Starch Glycolate	1: 2	76	0.1 N HCl Solution	Gould and Scott, 2005
6	Crospovidone (kneading method)	1: 2	76.5	0.1 N HCl Solution	Saharan *et al*., 2009
7	Crospovidone (Co-precipitation)	1: 2	26.25	0.1 N HCl Solution	Rasool *et al*., 2002
8	Polyvenyl pyrrolidone	1 : 20	93	0.1 N HCl Solution	Patel *et al*., 2008
9	D- α -tocopheryl polyethylene glycol 1000 succinate	1: 2	47.5	0.1 N HCl Solution	Chauling *et al*., 2009
10	Urea	1:5	25	pH = 3.0	Jain *et al*., 2010
11	Hydroxypropyl-Methylcellulose E50LV	1:2	55	pH = 3.0	Jain *et al*., 2010

dissolution medium (Zhi *et al*., 2005). In addition to the chitosan solution (aqueous phase), this formulation contained a surfactant (polyethylene glycol octylphenyl ether), oil phase (cyclohexane) and cosurfactant (*n*-hexanol). As chitosan possesses both hydroxyl and amine groups in its structure, it exhibits the possibility of strong interaction with the lipophilic molecules and it also possesses the capability of adsorbing the water-insoluble molecules like furosemide (Zhi *et al*., 2005).

Self-microemulsifying system (SMES) based attempts have also been made to enhance furosemide solubility (Zvonar *et al*., 2010). Zvonar *et al*. prepared SMES by mixing the carriers (surfactant and co-surfactant, Labrasol® and Plurol oleique® in 4:1 ratio) with different concentrations of mygliol 812® (triglyceride) to produce a homogeneous mixture (Zvonar *et al*., 2010). This mixture was then blended with different concentrations of $CaCl_2$ (0.02–0.5%, w/w) followed by the addition of variable quantities of thickening agent (white wax or colloidal silica) and polymer matrix (chitosan). Before thickening, furosemide was added to the mixture for the obtention of drug loaded SMES. The dissolution test of these SMES was carried in 0.1 N HCl and phosphate buffer pH 6.8. Faster drug release was achieved in phosphate buffer pH 6.8 compared to that of 0.1 N HCl (Zvonar *et al*., 2010). The SMES with 4% thickening agent and 5% furosemide showed highest release (72%) in 30 min possibly due to the formation of (micro) emulsion. On dilution with intestinal fluids, (micro) emulsion provides the drug in its dissolved form simulating an extensive surface area for drug absorption (Porter *et al*., 2007, Pouton, 2000). Despite solubility enhancement, presence of lipids and surfactants in the product supplies suitable conditions for bioavailability enhancement. In the presence of 0.2% (v/v) SMES, considerably increased permeability of furosemide was observed in all segments of the intestine and in caco-2 cell monolayers when compared to the analogous reference data. The furosemide permeability observed in the duodenum and jejunum in the presence of SMES were significantly (p<0.05) higher than that measured with SMES in the ileum. Labrasol® possesses

Table 4: Percentage of drug released from complexes of furosemide after 30 min

	Material used	Drug to Enhancer (s) Ratio	Drug Dissolved (%) After 30 min	Dissolution Medium	Ref.
1	β-cyclodextrin	1: 2	93	Phosphate Buffer (pH=5.8)	Patel *et al*., 2005
2	β-cyclodextrin	1: 1	42.5	0.1 N HCl solution	Ozdemir and Ordu, 1998
3	β-cyclodextrin	1: 4.5	100	0.1 N HCl solution	Patel *et al*., 2010
4	Hydroxyl propyl β-cyclodextrin	1: 4.5	96	Distilled Water	Vlachou and Papaioannou, 2003
5	Hydroxyl propyl β-cyclodextrin	1: 5.5	100	0.1 N HCl solution	Patel *et al*., 2010b
6	Mobile Crystalline Material	1: 0.72	81	0.1 N HCl Solution	Ambrogi *et al*., 2011
7	Hydrotalcite like compound	2: 1	72	pH = 3.0	Perioli *et al*., 2011

Table 5: Percentage of drug released from liquisolid formulations of furosemide after 30 min

	Material Used	Drug to Enhancer(s) ratio	Drug dissolved (%) after 30 min	Dissolution Medium	Ref.
1	Avicel PH 102: Aerosil 200 (10: 1)	--	98.35	0.1 N HCl solution	Burra and Galipelly, 2010
2	(Synperonic® PE/L 81) polyoxyethylene-polyoxypropylene-polyoxyethylene block Copolymer	1: 2	54	0.1 N HCl solution	Akinlade *et al*., 2010

Table 6: Percentage of drug released from microemulsion of furosemide after 30 min

	Material Used	Drug to Enhancer (s) Ratio	Drug Dissolved (%) After 30 min	Dissolution Medium	Ref.
1	Chitosan	--	24	Aqueous solution at pH =3.0	Zhi *et al*., 2005

capability of inducing nominal reversible pores in the tight junctions of gastrointestinal tract. Another reason for increased permeability could be the modified membrane fluidity and polar defects caused by surfactant Labrasol® which errand increased transcellular permeability of furosemide (Zvonar *et al*., 2010); however gastrointestinal tract disruption may cause some pathological disorders (Zvonar *et al*., 2010).

CONCLUSION

It is concluded from the results that dissolution rate increases by increasing enhancer quantity. Dissolution rate also depends upon the type of enhancer and dissolution medium. In order to achieve relatively enhanced value of DP_{30}, complexation by solvent evaporation is the best method using β-cyclodextrin. Solid dispersion is best if polyethylene glycol is used as enhancer along with microcrystalline cellulose as hydrophilic adsorbent because it gives DP_{30} value of 100%. Complexation with hydroxylpropyl β-cyclodextrin (1: 5.5) is also a good method as it proposed DP_{30}=100%. Many good techniques are still to be tried like co-crystallization. Future studies may be conducted using new techniques. All the approaches narrated in this article possess good perceptions for additional research, *in-vivo* studies should be carried out focusing on drug delivery system development.

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