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Formulation and development of fast dissolving oral film of a poorly soluble drug, frusemide with improved drug loading using mixed solvency concept and its evaluation

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ABSTRACT

The aim of the present research work is to explore the application of mixed solvency concept to formulate and develop a fast dissolving oral film of furosemide with improved drug loading. In the present study, poorly soluble drug, furosemide was tried to be solubilized by employing the combination of physiologically compatible water-soluble additives (solubilizers) to formulate its fast dissolving formulations. For the development of fast dissolving oral film, firstly, different film forming polymers were tested for their film properties. The second fast dissolving layer was also formed and optimized. Solubility studies were conducted to select water-soluble additives for formulation of fast dissolving drug layer. Keeping the total concentration less than 40 % w/v of mixed blends, different aqueous blends were prepared employing solubilizers from among sodium benzoate, sodium acetate, sodium citrate, urea, niacinamide, glycerin, propylene glycol, polyethylene glycol 200, polyethylene glycol 400, polyethylene glycol 600, and PVP K 30. Maximum solubility of furosemide was found in blends- F5 (10% sodium caprylate +2.5%sodium benzoate+ 2.5% niacinamide) and in blend F7 (10% sodium caprylate +2.5%sodium benzoate +2.5% sodium citrate + 2.5% niacinamide). Prepared films were evaluated for drug content, thickness, folding endurance, tensile strength and hydration ratio.

Keywords: Furosemide, fast dissolving oral film, mixed solvency concept.

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INTRODUCTION

Oral drug delivery is the most widely acceptable drug delivery system as it provides numerous advantages when compared to other drug delivery systems. But due to some limitations like lesser bioavailability of drug, longer onset time and dysphagia patients, manufacturers bend towards parenteral and liquid orals. Whereas liquid orals having the problem associated with accurate dosing and also painful for parenteral drug administration, which creates patient incompliance. There are three important factors for any drug product viz bioavailability, quicker action (if required) and patient compliance. So, each company wants to formulate the products which fulfils these three factors according to the patient's need to increase their market profile [1]. To provide maximum concentration at the site of action of drug and achieve therapeutic level and to maintain it is main aim of any drug delivery system.

Fast dissolving oral film (FDF)

This novel drug delivery system was introduced as a substitute for conventional oral dosage forms for patients who cannot swallow medicines easily, bed-prone patients, geriatric patients and pediatric patients. Orally disintegrating tablets are present in the market which gives disintegrating time of one to two minutes. Mouth dissolving films were then introduced which significantly marked an upgradation in the oral disintegrating drug delivery system. The various avenues explored for rapid drug releasing product, mouth dissolving film method is gaining much attention. [2]

Recently, the regulatory authorities have enlarged the variety of "oro mucosal preparations" by buccal films and oro dispersible films. The United States Food and Drug Administration (USFDA) use the term 'soluble film' for mouth dissolving films. The European Pharmacopoeia

(Ph.Eur.) monograph on oro mucosal preparations was updated in its 7.4 edition, including 'mucoadhesive preparation' and 'fast dissolving film'. Mouth dissolving films are described in the monograph as rapidly dispersing single or multilayer sheets of suitable material. [3]

Mouth dissolving films contain active molecules which are dissolved or dispersed in the film, the film is placed on a tongue of patient where it gets disintegrated and dissolves to release the drug for absorption. The problem of drug administration of certain groups of patients like paediatrics, geriatric, bedridden, nauseous or noncompliant patients, and scientists developed new dosage alternatives from oral route to keep these patients' group in mind and mouth-dissolving film is one of the alternative dosage forms of oral route.

Drug release mechanism of FDF

The mouth dissolving oral film is a very thin film placed on tongue, gets instantly wetted by saliva, disintegrates and dissolves rapidly to release drug. This released drug gets absorbed directly in to the systemic circulation by oral mucosa. Oral mucosal drug delivery is a potential site for drug administration. It provides rapid onset of action, enhanced bioavailability of drug and by passes pre-systemic elimination within GI tract. Oral mucosa is highly permeable and rich in blood supply, so the drug is directly absorbed into the blood circulation.

General composition of FDF [4]

Table 1: The fast dissolving film consists of general ingredients in the following quantities

S.No.	Ingredients list	Quantity (w/w)
1.	Drug	1-25%
2.	Water soluble polymer	40-50%
3.	Plasticizer	0-20%
4.	Saliva stimulating agent	2-6%
5.	Sweetening agent	3-6%
6.	Flavouring agent,	q.s.
7.	Surfactant	q.s.
8.	Colours	q.s.
9.	Filler	q.s.

Method of preparation of FDF [5]

There are five methods for the preparation of FDF: -

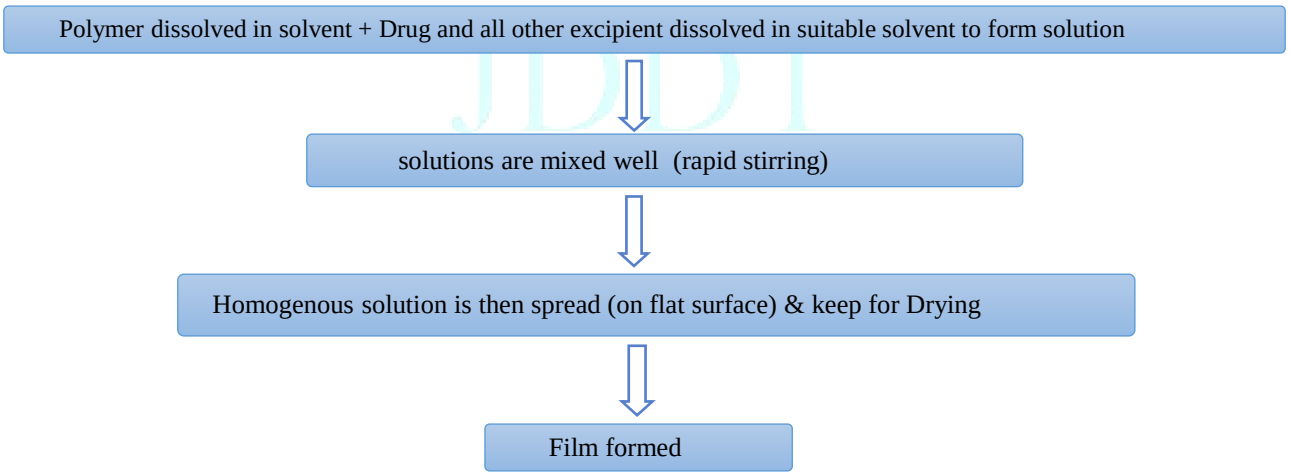
- Solvent casting
- Semisolid casting
- Hot melt extrusion
- Solid dispersion extrusion
- Rolling method

Solvent casting method: - In suitable solvent, water-soluble polymers are dissolved and in another suitable solvent, the drug along with other excipients is dissolved, then both solutions are mixed well and casted into the petri plate and kept for drying.

Mixed Solvency Concept

Maheshwari [6] proposed the concept of mixed-solvency concept and proved that all substances whether liquids, solids or gases may enhance the solubility of poorly-soluble drugs. He has carried out solubility studies on poorly-water soluble drug, salicylic acid (as model drug). Solubility studies were carried in the solutions containing hydrotropic agents (urea and sodium citrate), cosolvents (glycerin, propylene glycol, PEG 300 and PEG 400) and water-soluble solids (PEG 4000 and PEG 6000) individually as well as in 10 randomly prepared blends keeping total concentration constant i.e. 40%. Results showed that seven out of ten blends produced synergistic effect on solubility enhancement.

Several studies [7-29] have been conducted on various poorly soluble drugs using mixed solvency concept.



MATERIALS AND METHOD

Materials

Furosemide drug was obtained as a gift sample from IPCA Laboratories, Pithumpur. Other chemicals used were of analytical grade. Demineralized water was used in the study.

Method

Preparation of aqueous solutions of solubilizers

For the preparation of different blends of solubilizers (% w/v), sodium caprylate, niacinamide, sodium citrate, caffeine, PVP k 30, propylene glycol, PEG 200, PEG 400, PEG 600, glycerin etc. were weighed/ measured and taken in a volumetric flask and about 50 ml of DM water was added in this flask and was shaken to achieve complete dissolution of

solubilizers. Then, volume was made up to 100 ml by DM water. Total solute concentration was varied up to 40% w/v concentration and the % solubility of drug (furosemide) was calculated.

Solubility studies:

Solubility studies in different aqueous systems of solubilizers were carried out by equilibrium solubility method.

According to this method, 5 ml of respective medium was taken in a vial and excess amount of drug furosemide was added in above vial, kept it closed by rubber cap with aluminium seal, and was placed on a mechanical shaker at room temperature for 12 hours, and solution was allowed to equilibrate for 24 hours undisturbed. Then, the solution was filtered through filter paper. The filtrate was appropriately diluted with the respective aqueous medium and the absorbance of the solution was measured at 333 nm on a double beam UV/Visible spectrophotometer (Shimadzu 1700) against respective reagent blanks. The percent solubility was calculated using calibration curves.

Solubility of furosemide in different medium

Table 2: Drug solubility in different medium

S. No.	Solvent	Solubility of furosemide (mg/ml)	Solubility (% w/v)
1	D.M. water	0.0792	0.0079
2	0.1 N HCl	0.0570	0.0057
3	Buffer (pH 6.8)	1.6500	0.1650
4	A. 15% Propylene glycol	5.5470	0.5547
5	B. 15% Glycerin	14.6600	1.4660

Table 3: Solubility of drug in aqueous solutions containing solid solubilizers

S.No.	Blend	Aqueous blend of solubilizers	Ratio of solubilizer concentration (% w/v)	Solubility of furosemide (mg/ml)	Solubility (% w/v)
1	C	Sodium caprylate	20%	85.00	8.500
2	D	Sodium benzoate	20%	62.70	6.270

Table 4: Solubility of drug in aqueous solutions containing combinations of solubilizers

S.No.	Blend	Blends composition (w/v)	Solubility of furosemide (mg/ml)	Solubility (% w/v)
6	E	20%SC+5%SB+5%NM	125.68	12.568
7	F	20%SC+10%SA+5%$PVPK_{30}$	53.01	5.301
8	G	20%SC+10%SB+10%NM	121.51	12.151
9	H	10%SC+2.5%SB+2.5%NM	115.24	11.524
10	I	10%SC+10%SB+10%NM	57.21	5.721
11	J	20%SC+10%SB+5%NM	83.85	8.385
12	K	20%SC+5%SA+5%SCI	56.36	5.636
13	L	10%SC+10%SB+10%SA	36.17	3.617
14	M	10%SC+2.5%SB+2.5%NM+5% SCI	131.60	13.160
15	N	10%SC+2.5%SB+2.5%NM+2.5% SCI	124.36	12.436
16	O	20%SC+5%SB+5%NM+5% SA	91.86	9.186
17	P	20%SC+5%SB+5%NM+10% SA	Because of excess solubility, semi solid mass was produced and it could not be filtered to determine the solubility	--
18	Q	10%SC+2.5%SB+2.5%NM+10% SCI	Because of excess solubility, semi solid mass was produced and it could not be filtered to determine the solubility	--
19	R	20%SC+20%SB+10%NM	Because of excess solubility, semi solid mass was produced and it could not be filtered to determine the solubility	---
20	S	20%SC+5%SB+5%SA	Because of excess solubility, semi solid mass was produced and it could not be filtered to determine the solubility	---

Here- SC-Sodium caprylate, NM-Niacinamide, SB-Sodium benzoate, SCI-sodium citrate, SA-Sodium acetate

Selection of polymers

For selection of water-soluble film forming polymers, films of different polymers were prepared and their film properties were evaluated. As the important function of polymer was to provide mechanical strength and quick disintegration to the film, its selection was done taking physical strength and disintegration as the most important optimization parameters of the film.

Procedure:

For preparation of polymer films, 8.5 ml of blend containing 15% v/v glycerin (as plasticizer) was taken in a vial. Polymer (1.5 gm) was added and made up to 10 ml with blend, preparation was stirred properly and placed undisturbed for 5-6 hrs. The film of resulting polymer solution was casted in petri plate and was dried at 40ºC in hot air oven for 24 hours and then wrapped in aluminium foil and stored. The prepared films were evaluated for their film properties.

Evaluation of casted polymeric film

a) Disintegration time

Disintegration was tested by taking 25 ml of phosphate buffer (pH 6.8) in a Petri dish and a film was placed in it. Swirling of the buffer was done manually in every 10 seconds. Time required to completely break and disperse the film was noted as the disintegration time.

b) Folding endurance

Folding endurance was determined by repeatedly folding the film at the same position until it breaks. The number of times the films can be folded without breaking is termed as the folding endurance value.

c) Thickness

The thickness of film was determined by the use of micrometre (Digimatic micrometre, Mitutoyo, Tokyo, Japan) at five locations (centre and four corners) and mean thickness was calculated.

Table 5: Evaluation of film properties

S.no.	Polymer used	Appearance of film	Disintegration time (sec)	Thickness (mm)
1.	HPMC E-5	Transparent, smooth, thin, non-tacky, easily removed from Petri plate	45	0.09
2.	HPMC E-50	Transparent, smooth, thick, non-tacky, easily removed from Petri plate	100	0.23
3.	PVP K30	Semi-transparent, smooth, sticky and tacky	---	---
4.	Gelatine	Gummy film, transparent, sticky and tacky	---	---
5.	Starch	Whitish translucent, thick, brittle film	115	0.34
6.	CMC	Whitish translucent, thick, sticky	---	---

Optimization of concentration of polymer

Five batches of different selected polymer (HPMC E-5) concentrations were prepared, casted and their film properties were studied.

Table 6: Properties of different concentrations of HPMC E-5

S.No.	Selection factor	10% w/v HPMC E-5	12.5% w/v HPMC E-5	15% w/v HPMC E-5	17.5% w/v HPMC E-5	20% w/v HPMC E-5
1.	Viscosity of polymeric preparation	Less viscous	Less viscous	Viscous	Viscous	Viscous
2	Pourability	Easily pourable	Easily pourable	Pourable	Pourable	Difficult to pour
3.	Appearance of film and folding parameter	Transparent but easily break on folding	Transparent, little folding capacity	Transparent, with high folding capacity	Transparent with high folding capacity	Transparent but easily breakable
4.	Uniformity of film	Uniform	Uniform	Uniform	Uniform	Non-uniform
5.	Thickness	Thin 0.10 mm	Thin 0.12mm	Thin 0.09mm	Thin 0.11 mm	Thick 0.14 mm

Selection of plasticizer

The effect of glycerine, propylene glycol, polyethylene glycol as plasticizer was studied. Five batches of HPMC E-5 films were prepared with respective plasticizers used in concentration of 15% v/v and properties of casted films were evaluated.

Table 7: Effect of different plasticizers in polymeric casted film

S.No.	Polymer (15%w/v)	Plasticizer (15%v/v)	Appearance of film	Thickness (mm)	Folding endurance	Disintegration time (sec)
1.	HPMC E-5	PG	Thin, smooth, transparent, uniform	0.08	114	56
2.	HPMC E-5	Glycerine	Transparent, thickness is greater than first film, less smooth compared to first batch	0.07	157	40
3.	HPMC E-5	PEG 200	Smooth, transparent, thickness is greater than first film	0.11	126	44
4.	HPMC E-5	PEG 400	Non-uniform, thickness is greater, transparent	0.13	149	57
5.	HPMC E-5	PEG 600	Thickness is greater than first three batches, transparent	0.17	145	67

Here-HPMC-hydroxy propyl methyl cellulose, PEG -poly ethylene glycol, PG-propylene glycol.

Optimization of plasticizer concentration

Five batches of HPMC E-5 with different concentration range 5%-25% of selected plasticizer (Glycerine) were prepared and their film properties were studied.

Table 8: Effect of different concentrations of selected plasticizers in properties of polymeric film

S.No.	Polymer (15%w/v)	Glycerine Concentration (v/v)	Appearance of film	Thickness (mm)	Folding endurance	Disintegration time (sec)
1.	HPMC E-5	5%	Hard and brittle	0.12	23	43
2.	HPMC E-5	10%	Hard, uniform, transparent	0.10	61	49
3.	HPMC E-5	15%	Soft, smooth, uniform, transparent	0.07	177	39
4.	HPMC E-5	20%	Soft, sticky, transparent	0.15	145	44
5.	HPMC E-5	25%	Soft, very sticky	0.17	133	50

HPMC- hydroxypropyl methyl cellulose.

Selection of super disintegrants

Solutions of four different polymeric formulations of HPMC E-5 (15% w/v) were prepared with (15% v/v) glycerin and in each of this solution respective super disintegrant (0.3%w/v) was added and films were casted in Petri plates, after proper drying at 40°C for 24 hours then films were wrapped in aluminium foil with sealing plastic bags, stored and their film properties were studied.

Table 9: Effect of super disintegrant on the properties of polymeric film

S.No.	Polymer (15%w/v)	Plasticizer concentration (15% v/v)	Super disintegrant	Thickness (mm)	Disintegration time (sec)
1.	HPMC E-5	Glycerine	Croscarmellose sodium (ac-di-sol)	0.14	45
2.	HPMC E-5	Glycerine	Crosspovidone	0.06	37
3.	HPMC E-5	Glycerine	Microcrystalline cellulose (avicel)	0.15	64
4.	HPMC E-5	Glycerine	Sodium starch glycolate	0.17	53

Optimization of super disintegrant concentration

Solutions of four different polymeric formulations of HPMC E-5 (15% w/v) were prepared with (15% v/v) glycerine and in each of this solution cross povidone in different concentration range 0.3%-0.6% w/v were added in preparation and films were casted in Petri plate, after proper drying at 40°C for 24 hours then film were wrapped in aluminium foil with sealing plastic bags, stored and their film properties were studied.

Table 10: Effect of different concentrations of cross povidone on the properties of polymeric films

S.No.	Polymer (15%w/v)	Plasticizer conc. (15% v/v)	Crosspovidone (% w/v)	Thickness (mm)	Folding endurance	Disintegration time (sec)
1.	HPMC E-5	Glycerine	0.3%	0.09	166	37
2.	HPMC E-5	Glycerine	0.4%	0.06	173	29
3.	HPMC E-5	Glycerine	0.5%	0.12	164	34
4.	HPMC E-5	Glycerine	0.6%	0.11	170	38

Formulation of FDF of furosemide

According to the preliminary studies and studies of selection of excipients, for the preparation and optimization of fast dissolving film layer, 8 batches were designed and fast dissolving films of different 8 formulae (table 31) were prepared (on the basis of less individual concentration of solubilizers and greater solubility enhancement of drug.)

Table 11: Composition of blends used for formulation development

S.No.	Blend name	COMPOSITION				
		Sodium caprylate (w/v)	Sodium benzoate (w/v)	Niacinamide (w/v)	Sodium citrate (w/v)	Sodium acetate (w/v)
1	B1	20%	20%	10%	---	---
2	B2	20%	5%	---	---	5%
3	B3	20%	10%	5%	---	---
4	B4	10%	10%	10%	---	---
5	B5	10%	2.5%	2.5%	2.5%	---
6	B6	10%	2.5%	2.5%	5%	---
7	B7	10%	2.5%	2.5%	----	---
8	B8	20%	5%	5%	----	5%

Table 12: Composition of formulation of fast dissolving films

S.No.	Batch code	Drug furosemide (mg)	Blends	Polymer HPMC E-5 (%w/v)	Plasticizer (% v/v)	Super disintegrants (% w/v)
1.	F1	500	B1	15%	15%	0.4%
2.	F2	500	B2	15%	15%	0.4%
3.	F3	500	B3	15%	15%	0.4%
4.	F4	500	B4	15%	15%	0.4%
5.	F5	500	B5	15%	15%	0.4%
6.	F6	500	B6	15%	15%	0.4%
7.	F7	500	B7	15%	15%	0.4%
8.	F8	500	B8	15%	15%	0.4%

Method of preparation of FDF of furosemide

500 mg furosemide was accurately weighed and dissolved in 8.5ml of respective solubilizer blend containing 15% v/v glycerine (as plasticizer). fourty mg crospovidone (as super disintegrant) and 1.5 gm of HPMC E-5 (as film forming polymer) were added and made up to 10 ml with blend. Preparation was properly mixed in blend and placed undisturbed for 5-6 hour. Then calculated volume of polymeric preparation were uniformly spread in Petri plate and dried in oven at temperature 40°C for 24 hrs. After proper drying, films were cut into desired calculated dimension i.e. 2.0×2.0 cm^2 in which 20 mg of furosemide was present. At last it was wrapped in an aluminium foil with sealing plastic bag and stored for further evaluations of film.

Dose calculation of drug: -

Outer diameter of Petri plate = 5.5 cm
Inner diameter of Petri plate = 5.2 cm
Inner radius of Petri plate = 5.2/2 cm = 2.6 cm
Inner area of Petri plate = area of circle= πr^2
$= 3.14\times (2.6)^2$
$= 21.2264\ cm^2$

10 ml of polymeric preparation contains 500mg of drug.

Therefore 2 ml of polymeric preparation contains 100 mg of drug.

This 2 ml polymeric preparation was spread over 21.2264 cm^2 area of Petri plate.

Therefore, 100 mg of drug is present in 21.2264 cm^2 area of Petri plate.

So, 20 mg present in.... = (21.2264 cm^2 / 100 mg) ×20 mg
= 4.24528 cm^2 area

Area of circle = area of square = a^2 (a= length of side of square)

$4.24528\ cm^2 = a^2$
$a = \sqrt{4.24528\ cm^2}$
$a = 2.06$ cm

By this calculation 20 mg dose of drug present in 2.0×2.0 cm^2 area of film.

Evaluation studies of fabricated FDF

a) In vitro dissolution rate study

Films containing 20 mg of furosemide were used in the in vitro dissolution study. Dissolution studies were conducted in USP II apparatus (paddle type) at 50 rpm, using 900 ml of 0.1 N HCl and 300 ml of simulated saliva fluid (2.38 gm Na_2HPO_4, 0.19 gm KH_2PO_4, and 8.00 gm NaCl per litre of distilled water adjusted with phosphoric acid to pH 6.8) as dissolution media. The temperature was maintained at 37±0.5° C. Ten ml samples were withdrawn at regular intervals and analyzed spectrophotometrically (Shimadzu A-160) at 333 nm after appropriate dilution with 0.1 N HCl and simulated saliva fluid respectively. Absorbances were noted against respective reagent blanks (placebo). An equal amount of fresh dissolution media was replaced immediately after each withdrawal of sample.

b) % Drug content determination

It was determined by taking one film theoretically equivalent to 20mg of drug and transferred in 1000 ml volumetric flask and approximately 400 ml of DM water was added to it. Flask was shaken for 15 minutes and volume was made up to the mark with DM water. The resulting solution was filtered and analyzed spectrophotometrically at 333 nm and drug content was determined.

% drug content= (practical value/ theoretical value) × 100

c) Surface pH

Film was taken and placed in a Petri plate containing 5 ml of water. After wetting of the film, the surface pH of the film was checked by using pH electrode.

d) Thickness

The thickness of film was determined by the use of micrometre (Digimatic micrometre, Mitutoyo, Tokyo, Japan) at five locations (centre and four corners) and mean thickness was calculated.

Table 13: Evaluation of formulated film batches

S.No.	Batch code	Mean thickness (mm)	Folding endurance	Disintegration time (sec)
1.	F1	0.14	153	37
2.	F2	0.19	169	34
3.	F3	0.09	157	37
4.	F4	0.11	152	45
5.	F5	0.04	175	26
6.	F6	0.12	142	36
7.	F7	0.03	178	27
8.	F8	0.13	155	30

In vitro dissolution rate study-Films containing 20 mg of furosemide were used in the in vitro dissolution study. Dissolution studies were conducted in USP II apparatus (paddle type) at 50 rpm, using 900 ml of 0.1 N HCl and 300 ml of simulated saliva fluid (2.38 gm Na_2HPO_4, 0.19 gm KH_2PO_4, and 8.00 gm NaCl per litre of distilled water adjusted with phosphoric acid to pH 6.8) as dissolution media. The temperature was maintained at 37±0.5˚ C. Ten ml samples were withdrawn at regular intervals and analysed spectrophotometrically (Simadzu A-160) at 333 nm after appropriate dilution with 0.1 N HCl and simulated saliva fluid respectively. Absorbance was noted against respective reagent blanks (placebo). An equal amount of fresh dissolution media was replaced immediately after each withdrawal of sample.

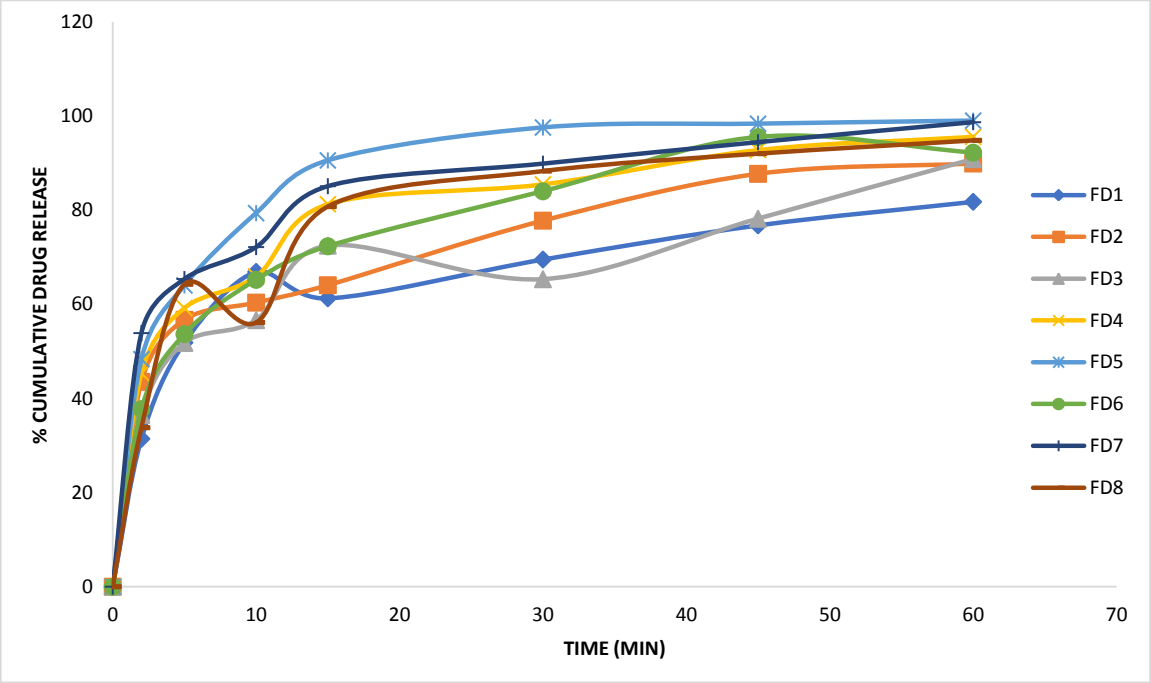


Figure 1: Graphical representation of % cumulative drug release v/s time plot in phosphate buffer of pH 6.8

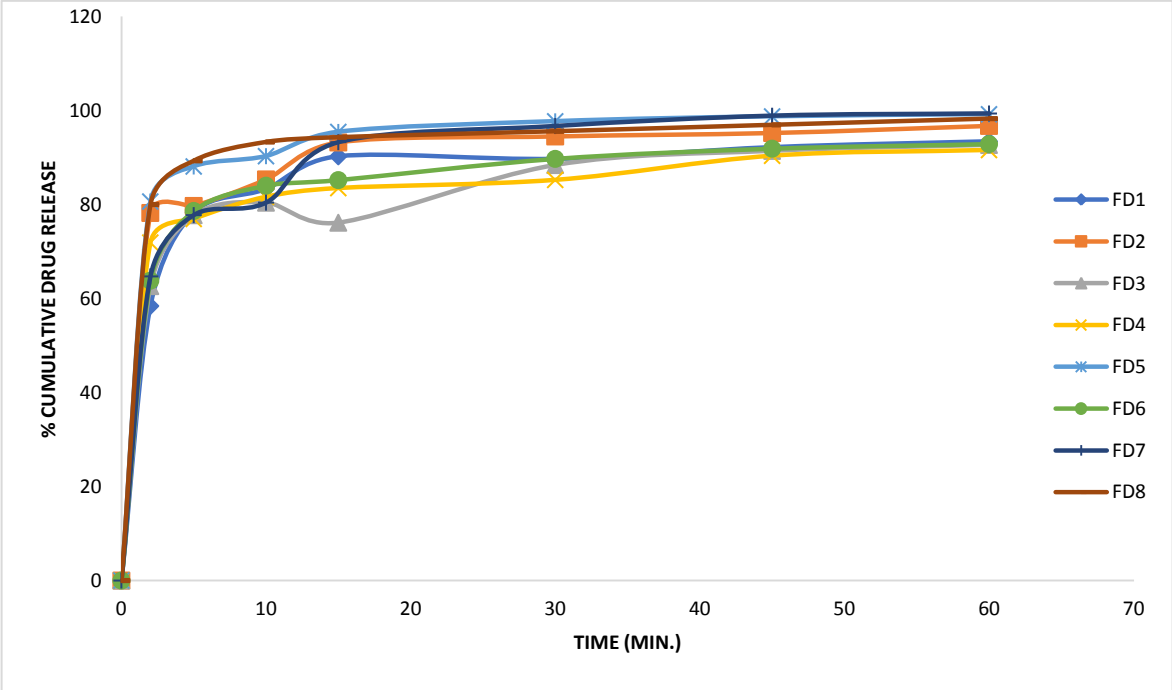


Figure 2: Graphical representation of % cumulative drug release v/s time plot in 0.1 N HCl

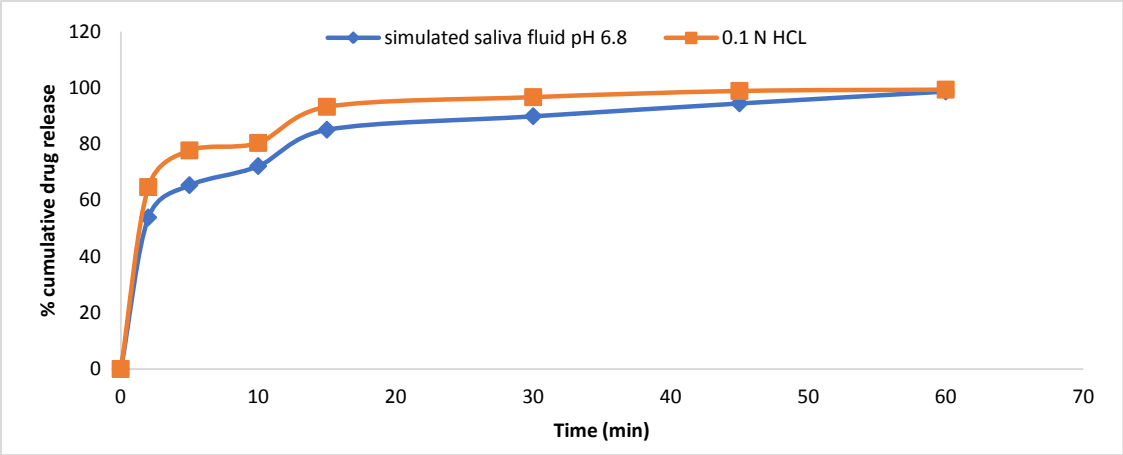


Figure 3: In-vitro dissolution profile of optimized batch FD5

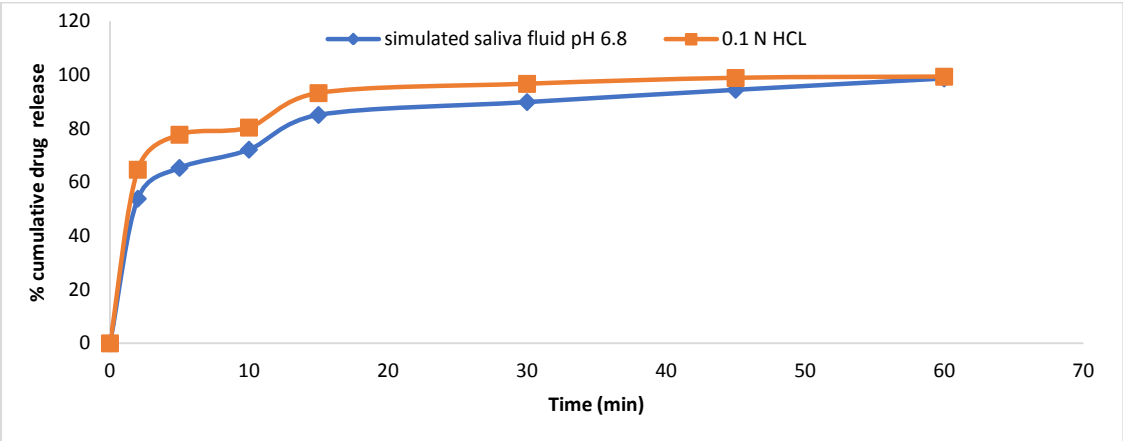


Figure 4: In-vitro dissolution profile of optimized batch FD7

Stability study of optimized batch FD5 and FD7

Stability study of optimized film formulation was carried out for two months at room temperature and refrigerated temperature.

Table 14: Stability studies of final optimized batch FD5

Stability condition	Sampling interval (days)	Evaluation parameters for Batch FD5		
		% Drug content	Surface pH	Thickness (mm)
Room temperature	0	99.78	6.80	0.01
	7	99.43	6.80	0.01
	14	98.73	6.82	0.01
	21	98.38	6.83	0.01
	28	98.04	6.85	0.01
	35	97.69	6.87	0.01
	42	97.34	6.88	0.01
	49	96.64	6.88	0.01
	56	96.30	6.90	0.01
	63	95.95	6.91	0.01
	70	95.56	6.93	0.01
Refrigerated temperature	0	99.64	6.80	0.01
	7	98.32	6.80	0.01
	14	98.38	6.80	0.01
	21	97.69	6.81	0.01
	28	97.34	6.82	0.01
	35	96.99	6.85	0.01
	42	96.64	6.88	0.01
	45	95.95	6.89	0.01
	56	95.56	6.89	0.01
	63	94.90	6.90	0.01
	70	94.56	6.91	0.01

Table 15: Stability studies of final optimized batch FD7

Stability condition	Sampling interval(days)	Evaluation parameters for Batch FD7		
		% Drug content	Surface pH	Thickness (mm)
Room temperature	0	99.82	6.80	0.01
	7	99.08	6.80	0.01
	14	98.46	6.81	0.01
	21	98.32	6.83	0.01
	28	98.04	6.83	0.01
	35	97.63	6.84	0.01
	42	96.99	6.85	0.01
	49	96.64	6.88	0.01
	56	95.99	6.90	0.01
	63	95.25	6.91	0.01
	70	94.90	6.92	0.01
Refrigerated temperature	0	99.43	6.80	0.01
	7	98.73	6.80	0.01
	14	98.38	6.81	0.01
	21	98.21	6.83	0.01
	28	97.63	6.85	0.01
	35	96.69	6.87	0.01
	42	96.32	6.88	0.01
	45	96.28	6.88	0.01
	56	95.76	6.90	0.01
	63	95.56	6.93	0.01
	70	94.54	6.96	0.01

RESULTS AND DISCUSSION

For the selection of solubilizers for increasing the solubility of drug (furosemide), solubility studies were conducted at room temperature in various solutions containing individual solubilizer or in combination of solubilizers blend. The solubility of furosemide was increased up to 11.52 % (w/v) in solubilizer in Blend F5 (10% sodium caprylate +2.5%sodium benzoate+ 2.5% niacinamide) and in Blend F7 (10% sodium caprylate +2.5%sodium benzoate +2.5% sodium citrate + 2.5% niacinamide) up to 12.43 % (w/v) that was maximum among all the blends. In order to minimize the probable toxic effects of individual solubilizer at high concentration, the blends of solubilizers were tried to give the expected solubility. The blends of solubilizers of total strength 15% and 17.5% w/v were used in selected final blends to get sufficiently expected solubilities. The maximum synergistic effect was observed in the blend containing sodium caprylate, sodium benzoate, niacinamide, sodium acetate, sodium citrate.

For the development of fast dissolving film, different film forming polymers, plasticizers, super disintegrants were tested. According to the mechanical properties and disintegration time of film, they were selected and optimized. HPMC E-5 15% w/v was taken as optimized concentration of polymer. On the basis of film properties, 15% v/v concentration of glycerine (as plasticizer) was optimized and selected. Crosspovidone in concentration of 0.4% w/v was optimized because of desired thickness and desired disintegration time (< 30 sec).

From selected and optimized ingredients, eight batches of fast dissolving film containing 20 mg dose of drug per 4 cm^2 were developed and evaluated for thickness, folding endurance, disintegration time and in-vitro dissolution profile. Amongst all the batches, FD5 and FD7 batch of prepared fast dissolving films showed better in vitro dissolution profile, disintegration time and were selected for stability studies. They were found quiet stable for 2 months.

CONCLUSION

From all the above studies, it was concluded that the approach of mixed solvency is novel, safe, cost-effective and user friendly. It also eliminates the problem of toxicity associated with high concentration of single solubilizers. So, it may be employed in dosage form development of drugs where fast onset of action is desired. It may also enhance the bioavailability associated with poor dissolution of drug.

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