WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.074
Volume 7, Issue 6, 484-499. Research Article ISSN 2277– 7105

FORMULATION DEVELOPMENT OF MODEL FAST DISSOLVING ORAL FILM OF A POORLY SOLUBLE DRUG WITH IMPROVED DRUG LOADING USING MIXED SOLVENCY CONCEPT AND ITS EVALUATION

Neha Sonkeshariya* and R. K. Maheshwari

Department of Pharmacy, Shri G.S. Institute of Technology and Science,
Park Road, Indore-452 003, Madhya Pradesh, India.

Article Received on
21 Jan. 2018,
Revised on 11 Feb. 2018,
Accepted on 04 March 2018,
DOI: 10.20959/wjpr20186-10981

***Corresponding Author**
Neha Sonkeshariya
Department of Pharmacy, Shri G.S. Institute of Technology and Science, Park Road, Indore-452 003, Madhya Pradesh, India.

ABSTRACT

The present study was aimed to develop a fast dissolving oral film containing ondansetron hydrochloride dihydrate (as model drug) with enhanced drug loading, which was achieved by improving drug solubility and reducing the total surface area of oral film using mixed solvency concept. HPMC E-5 as film forming polymer, propylene glycol as plasticizer and crospovidone as superdisintegrant were optimized and selected on the basis of thickness, disintegration time and mechanical properties of film. Initially solubility of ondansetron hydrochloride dihydrate was enhanced in aqueous solution by using various solubilizers like niacinamide (NM), sodium citrate (SC), PVP K_{30}, caffeine, HP beta cyclodextrin, PEG 4000, PEG 200, PEG 400, PEG 600, propylene glycol (PG), glycerin etc, individually and as combinations of four and five solubilizers. The maximum solubility of ondansetron hydrochloride dehydrate 13.63% w/v was achieved in 27% w/v mixed solvent system containing 15% v/v propylene glycol + 3% w/v NM + 3% w/v PVP K_{30} + 3% w/v SC + 3% w/v caffeine. Petriplate method was used for casting the polymeric film. Evaluation of prepared formulation was carried out including thickness, folding endurance test, disintegration time, in-vitro dissolution test, drug content, surface pH test and stability test.

KEYWORDS: Ondansetron hydrochloride dehydrate (O), niacinamide (NM), sodium citrate (SC), propylene glycol (PG), fast dissolving film (FDF).

INTRODUCTION

Among all dosage forms 60% dosage forms are oral solid dosage forms and they are highly accepted by the patients.[1] But there are some groups of patients who feel difficulty to administer oral dosage forms, for example- pediatric, geriatric, bedridden, nauseous or noncompliant patients. Scientists developed new dosage alternatives for oral route to keep these patients group in mind and mouth dissolving film is one of the alternative dosage forms of oral route. It was developed based on the technology of "transdermal patch". The mouth dissolving film also called as fast dissolving film (FDF), rapid film, or rapid disintegrating film/ strip.[2]

The mouth dissolving film is a very thin film placed on the 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.[2]

Fast dissolving film gives various advantages over conventional dosage forms and fast dissolving tablets. It avoids the problem of swallowing of tablets, does not require water for swallowing the dosage form, highly convenient at the time of travelling, produce rapid onset of action, bypasses first pass metabolism, avoids risk of chocking & suffocation, provides patient compliance. But fast dissolving films have some limitation like small dose loading and require special packaging.[3][4]

General composition of fast dissolving film[5]

- Drug (1 -25 %)
- Water soluble polymer (40-50 %)
- Plasticizer (0-20 %)
- Fillers, colour, flavour etc. (0-40 %)

Method of preparation of FDF[4]

There are five methods for the preparation of FDF

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

Solvent casting was used for making fast dissolving film in this project work.

In this research work, ondansetron hydrochloride dihydrate was used as a model drug and for increasing the solubility of poorly water soluble drug (ondansetron hydrochloride dihydrate) mixed solvency concept was used in place of organic solvent, which is a novel concept to enhance the solubility of the drug in the solvent medium with the aid of solubilizers in combination and by this technique the limitation of drug loading in FDF can be avoided.

The concept of mixed solvency proposed by Dr. R. K. Maheshwari states that each and every substance present in the universe has got solubilizing property i.e. all the liquids, gases and solids possess solubilizing power. As per his statement, each substance is a solubilizer. A concentrated aqueous solution containing various water soluble substances may act as good solvent for poorly water soluble drugs. Such concentrated solutions may show synergistic or additive solubilizing actions of solubilizers present in the solution for a particular solute.[6] For example solubility of ibuprofen has been enhanced by 47.46 folds in a 40% w/v mixed blend of PEG 400 (10% v/v) + PEG 300 (10% w/v) + Urea (10% w/v) + Sodium citrate (10% w/v).[7] Similarly, solubility of salicylic acid was also enhanced by more than 54 fold in a mixed blend of PEG 300 (10% v/v) + PEG 400 (10% v/v) + glycerin (10% v/v) + Sodium citrate (10% w/v), in 40% w/v total concentration. The solubilities of several water insoluble drugs have been enhanced by mixed solvency concept.[8][21]

Present study was aimed to enhance drug loading by incorporating large dose of drug in polymer matrix by oral dose of drug keeping in mind. For showing drug loading, area of film was reduced to half as compared to marketed ondansetron hydrochloride dihydrate oral film of same dose (4 mg).

MATERIALS AND METHOD

Materials

Ondansetron hydrochloride dihydrate was obtained as a gift sample from Modern Laboratories Ltd., Indore, India. Other chemicals like super disintegrants, plasticizers, solubilizers, polymers used were of analytical grade. Demineralised water was used in the study.

METHOD

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 mediums were taken in vials and excess amount of drug (ondansetron hydrochloride dihydrate) was added in above vials. Vials were closed by rubber caps with aluminium seals, and were placed on a mechanical shaker at room temperature for 12 hrs. Solutions were allowed to equilibrate for 24 hrs undisturbed. Then, the solutions were centrifuged and filtered through Whatman filter papers no. 41. The filtrates were appropriately diluted with the respective aqueous mediums and the absorbances of the solutions were measured at 310 nm on a double beam UV/Visible spectrophotometer (Simadzu 1700) against respective reagent blanks. The percent solubilities were calculated using the respective calibration curves.

For the preparation of different blends of solubilizers (% w/v), niacinamide, sodium citrate, caffeine, HP beta cyclodextrin, PVP $k_{30(\text{film forming polymer})}$, PEG 4000, PEG 6000, propylene glycol, PEG 200, PEG 400, PEG 600, glycerin etc. were weighed/ measured and taken in a volumetric flask and about 50 ml of D.M. water was added in this flask and was shaken to achieve complete dissolution of solubilizers. Then volume was made up to 100 ml by D.M. water. Total solute concentration was varied up to 40% w/v concentration and the % solubility of drug (ondansetron hydrochloride dihydrate) was calculated.

To decrease the individual concentration of solubilizers as well as individual toxicity of solubilizers, combinations of solubilizers in blends were used to increase the solubility of drug in various ratios.

Solubility enhancement ratio = Solubility of drug in solution containing solubilizers /Solubility of drug in demineralised water.

Preparation of fast dissolving film

125 mg Ondansetron hydrochloride dihydrate (equivalent to 100 mg of ondansetron) was accurately weighed and dissolved in 1ml of respective solubilizer blend in a vial. Then 15% v/v propylene glycol (as plasticizer), 0.4% w/v crospovidone (as superdisintegrant) and respective concentration (20 or 15% w/v) of HPMC E-5 (as film forming polymer) were added and properly mixed and volume was made up to 10ml with D.M. water. The preparation was placed undisturbed for 5-6 hrs (for complete and proper swelling of polymer)

and then calculated volume of polymeric preparations were uniformly spread in petriplates 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 4mg of ondansetron hydrochloride dihydrate was present. At last it was wrapped in an aluminium foil with sealing plastic bag and stored for further evaluations.

Dose calculation of drug

Outer diameter of petriplate = 5.5 cm

Inner diameter of petriplate = 5.1 cm

Inner radius of petriplate = 5.1/2 cm = 2.55 cm

Inner area of petriplate = area of circle $= \pi r^2$

= 3.14× $(2.55)^2$

= 20.41785 cm^2

10 ml of polymeric preparation contains 100mg of drug.

Therefore 2 ml of polymeric preparation contains 20mg of drug.

This 2 ml polymeric preparation was spread over 20.41785 cm^2 area of petriplate.

Therefore, 20mg of drug is present in 20.41785 cm^2 area of petriplate.

So, 4mg present in…..= (20.41785 cm^2/20mg) ×4mg

= 4.08357 cm^2 area

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

4.08357 cm^2 = a^2

a = $\sqrt{4.08357}cm2$

a = 2 cm

By this calculation 4mg dose of drug present in 2.0×2.0 cm^2 area of film.

Evaluation of films

a) Disintegration time

For orally disintegrating tablets disintegration time limit is 30 seconds or less described in CDER guidance and it can be applied to fast dissolving oral strips. Although, no official guidance is available for oral fast disintegrating films, this may be used as a qualitative guideline for quality control test at development stage. Disintegration time for film is 5-30 sec. there are two methods for conducting disintegration test of film in less media.

Slide frame method

One drop of distilled water was dropped by a pipette onto the oral films. Therefore the films were clamped into slide frames and were placed planar on a Petridish. The time until the film dissolved and caused a hole within the film was measured.

Petri dish methods

2 ml of distilled water was placed in a petridish and one film was put on the surface of the water and the time measured until the oral film was dissolved completely. "Petridish method was used for conducting disintegration test of film".

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 micrometer (Digimatic micrometer, Mitutoyo, Tokyo, Japan) at five locations (center and four corners) and mean thickness was calculated.

d) In-vitro dissolution test

Dissolution tests of ondansetron hydrochloride dihydrate films containing 4mg drug were performed by using USP II apparatus (rotating paddle apparatus) at 50 rpm with 900 ml 0.1 N HCl or phosphate buffer of pH 6.8 as dissolution medium. The temperature of dissolution medium was maintained at 37± 0.5°C. Ten ml of dissolution media was withdrawn at regular intervals and fresh media was replaced immediately after withdrawal of sample. The sample was filtered, diluted when ever required, analysed in U.V. at 310nm and absorbance was noted against reagent blank.

e) % Drug content determination

It was determined by taking one film (ondansetron hydrochloride dihydrate 4mg) in 500 ml volumetric flask and dissolved in sufficient amount phosphate buffer of pH 6.8 and after complete dissolution volume was made upto the mark with phosphate buffer of pH 6.8. Absorbance was noted at 310 nm and % drug content with respect to 4 mg/ 4cm^2 was calculated.

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

f) Surface pH

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

g) Stability study

Stability study of optimized film formulation was carried out for two month at 40°C±2°C/ 75% RH±5% RH (accelerated) and 25°C±2°C/ 60%RH± 5%RH (room temperature).

RESULTS AND DISCUSSION

On the basis of solubility studies, combinations of five solubilizer's aqueous blends were selected for dissolving drug because of low individual toxicity of solubilizer and achieved desired required solubility of drug described in table 7 & 8. For formulation development HPMC E5 (15% w/v & 20% w/v), propylene glycol (15% v/v) and crospovidone (0.4% w/v) were optimized and selected on the basis of mechanical properties and disintegration time of film. Eight batches of optimised formulation were made described in table 9. Evaluations of eight batches were performed described in table 10 & fig 1, 2, 3. Among eight batches, F_6 batch showed better evaluation results and was selected for stability studies. It was found to be stable for 2 months described in table 11. F_6 batch was compared with the marketed formulation (Emifilm 4 mg) and was found to be comparable with the parameters of marketed formulation described in table 12 & fig 4, 5 whereas the area of formulated film F_6 (4mg/4cm^2) was half of the area of marketed film product (4mg/8cm^2).

Table 1: Calibration curve of ondansetron hydrochloride dihydrate in different media.

S.no.	Media	Regression equation	Correlation coefficient
1.	D.M. water	y = 0.048x + 0.010	R^2 = 0.997
2.	Phosphate buffer of pH 6.8	y = 0.049x + 0.008	R^2 = 0.999
3.	0.1 N HCl	y = 0.049x + 0.000	R^2 = 0.999

Table 2: Solubility of drug in aqueous solutions containing liquid solubilizers.

S.no.	Aqueous blend of solubilizers	Concentration (% w/v)	Solubility (mg/ml)	Solubility (% w/v)	Solubility enhancement ratio
1.	D.M. water	---	0.072	0.0072	---
2.	Propylene glycol	15	40.00	4.00	555
3.	PEG 200	15	11.86	1.19	164
4.	PEG 400	15	12.28	1.23	170
5.	PEG 600	15	23.47	2.35	325
6.	Glycerin	15	7.12	0.71	98

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

S.no.	Aqueous blend of solubilizer	Concentration (% w/v)	Solubility (mg/ml)	Solubility (% w/v)	Solubility enhancement ratio
1.	PVP K_{30}	10	39.57	3.96	549
2.	Niacinamide	10	62.94	6.29	874
3.	PEG 4000	10	31.05	3.11	431
4.	Sodium citrate	10	45.20	4.52	627
5.	HP beta cyclo-dextrin	10	12.00	1.20	166
6.	Caffeine + PG	10:5	54.96	5.5	763
7.	Sodium acetate	10	Readily formed precipitate		
8.	Sodium caprylate	10	Readily formed precipitate		
9.	Sodium benzoate	10	Precipitate formed		
10.	Benzoic acid + PG	2:5	Readily forms precipitate		

PEG 4000- poly ethylene glycol 4000, PG-propylene glycol, PVP k_{30}- polyvinyl pyrrolidone grade k_{30}.

Table 4: Solubility of drug in aqueous solutions containing two solubilizers.

S.no.	Aqueous blend of solubilizer	Ratio of solubilizer concentration (% w/v)	Solubility (mg/ml)	Solubility (% w/v)	Solubility enhancement ratio
1.	PG + PVP K_{30}	15:15	71.00	7.10	986
2.	PG + NM	15:20	150.02	15.00	2083
3.	PG + HP beta cyclo-dextrin	15:10	52.43	5.24	727
4.	PG + SC	15:10	85.62	8.56	1188
5.	PG + caffeine	15:5	94.72	9.47	1315
6.	PG + PEG 4000	15:10	69.08	6.91	959

PEG 4000- poly ethylene glycol 4000, PG-propylene glycol, NM-niacinamide, PVP k_{30}-polyvinyl pyrrolidone grade k_{30}, SC-sodium citrate.

Table 5: Solubility of drug in aqueous solutions containing three solubilizers.

S.no.	Aqueous blend of solubilizer	Ratio of solubilizer concentration (% w/v)	Solubility (mg/ml)	Solubility (% w/v)	Solubility enhance-ment ratio
1.	PG + NM + HP beta cyclo-dextrin	15:10:10	108.27	10.83	1504
2.	PG + NM + SC	15:10:10	145.06	14.51	2015
3.	PG + caffeine + NM	15:10:10	148.82	14.88	2066
4.	PG + PVP K_{30} + NM	15:10:10	133.51	13.35	1854
5.	PG + PVP K_{30} + PEG 4000	15:10:10	107.45	10.75	1493
6.	PG + caffeine + PEG 4000	15:10:10	127.38	12.74	1769
7.	PG + NM + PEG 4000	15:10:10	135.04	13.50	1875
8.	PG + SC + PEG 4000	15:10:10	114.62	11.46	1591
9.	PG + PVP K_{30} + caffeine	15:10:10	127.93	12.79	1776

PEG 4000- poly ethylene glycol 4000, PG-propylene glycol, NM-niacinamide, PVP k_{30}-polyvinyl pyrrolidone grade k_{30}, SC-sodium citrate.

Table 6: Solubility of drug in aqueous solutions containing four solubilizers.

S.no.	Aqueous blend of solubilizer	Ratio of solubilizer concentration (% w/v)	Solubility (mg/ml)	Solubility (% w/v)	Solubility enhancement ratio
1.	PG + HP beta CD+ SC + caffeine	15:5:5:5	90.08	9.01	1251
2.	PG + caffeine +SC + PEG 4000	15:5:5:5	101.61	10.16	1411
3.	PG + SC +PEG 4000 + NM	15:5:5:5	112.50	11.25	1562
4.	PG + PEG 4000 + NM + PVP K_{30}	15:5:5:5	104.87	10.49	1456
5.	PG + PEG 4000 + SC + HP beta CD	15:5:5:5	84.13	8.41	1168

PEG 4000- poly ethylene glycol 4000, PG-propylene glycol, NM-niacinamide, PVP k_{30} polyvinyl pyrrolidone grade k_{30}, SC-sodium citrate, HPB CD-HP beta cyclo-dextrin.

Table 7: Solubility of drug in aqueous solutions containing five solubilizers.

S.No.	Aqueous blend of solubilizer	Ratio of solubilizer concentration (% w/v)	Solubility (mg/ml)	Solubility (% w/v)	Solubility enhance-ment ratio
1.	PG + NM + PVP K_{30} + SC + caffeine	15:3:3:3:3	136.33	13.63	1893
2.	PG + NM + SC + PVP K_{30} + PEG 4000	15:3:3:3:3	94.00	9.40	1305
3.	PG + NM + SC + caffeine + PEG 4000	15:3:3:3:3	134.29	13.43	1865
4.	PG + SC + caffeine + PVP K_{30} + PEG 4000	15:3:3:3:3	112.67	11.27	1565
5.	PG + NM + caffeine + PVP K_{30} + PEG 4000	15:3:3:3:3	128.34	12.83	1781

PEG 4000- poly ethylene glycol 4000, PG-propylene glycol, NM-niacinamide, PVP k_{30}-polyvinyl pyrrolidone grade k_{30}, SC-sodium citrate, HPB CD-HP beta cyclo-dextrin.

Table 8: Optimized blend for formulation development.

S.no.	Blend name	Composition of blends
1.	B_1	15% PG + 3% NM + 3% SC + 3% caffeine + 3% PEG 4000
2.	B_2	15% PG + 3% NM + 3% PVP K_{30} + 3% SC + 3% caffeine
3.	B_3	15% PG + 3% SC + 3% caffeine + 3% PVP K_{30} + 3% PEG 4000
4.	B_4	15% PG + 3% NM + 3% caffeine + 3% PVP K_{30} + 3% PEG 4000

PEG 4000- poly ethylene glycol 4000, PG-propylene glycol, NM-niacinamide, PVP k_{30}-polyvinyl pyrrolidone grade k_{30}, SC-sodium citrate.

Table 9: Optimized batch formula of fast dissolving film.

S.no.	Batch code	Drug (ondan-setron Hydro-chloride dihydrate)	1 ml of blend	Polymer (HPMC E-5) (% w/v)	Plasticizer (propyl-ene glycol) (% v/v)	Superdis-integrant (crospo-vidone) (% w/v)	Volume made up by D.M. water
1.	F_1	100 mg	B_1	20%	15%	0.4%	10 ml
2.	F_2	100 mg	B_2	20%	15%	0.4%	10 ml
3.	F_3	100 mg	B_3	20%	15%	0.4%	10 ml
4.	F_4	100 mg	B_4	20%	15%	0.4%	10 ml
5.	F_5	100 mg	B_1	15%	15%	0.4%	10 ml
6.	F_6	100 mg	B_2	15%	15%	0.4%	10 ml
7.	F_7	100 mg	B_3	15%	15%	0.4%	10 ml
8.	F_8	100 mg	B_4	15%	15%	0.4%	10 ml

Table 10: Evaluation of formulated film batches (n=3).

S.no.	Batch code	Thickness (mm) ± S.D.	Folding endurance ±S.D.	Disintegration time (sec) ±S.D.
1.	F_1	0.092 ± 0.04	151±1.27	31±0.52
2.	F_2	0.088 ± 0.03	156±2.39	27±1.04
3.	F_3	0.128 ± 0.07	157±1.16	28±0.67
4.	F_4	0.132 ± 0.05	160±2.23	28±1.02
5.	F_5	0.112 ± 0.05	155±1.75	30±0.57
6.	F_6	0.074 ± 0.01	162±2.18	27±0.49
7.	F_7	0.100 ± 0.02	154±1.54	30±0.15
8.	F_8	0.091 ± 0.06	157±1.94	29±0.38

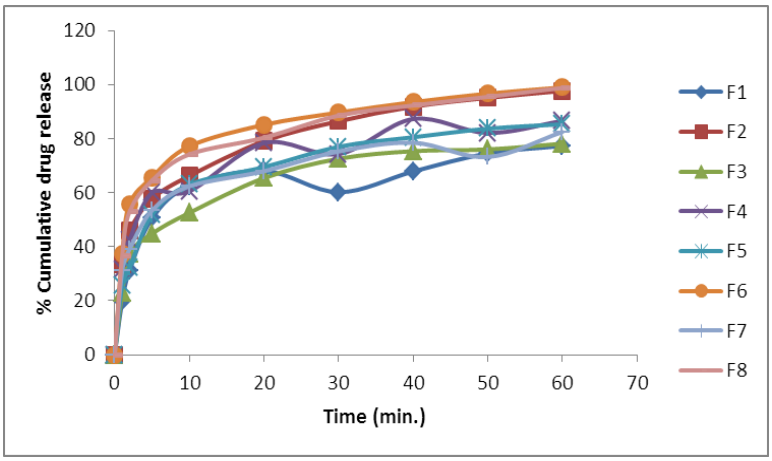

Fig. 1: Graphical representation of % cumulative drug release in phosphate buffer of pH 6.8.

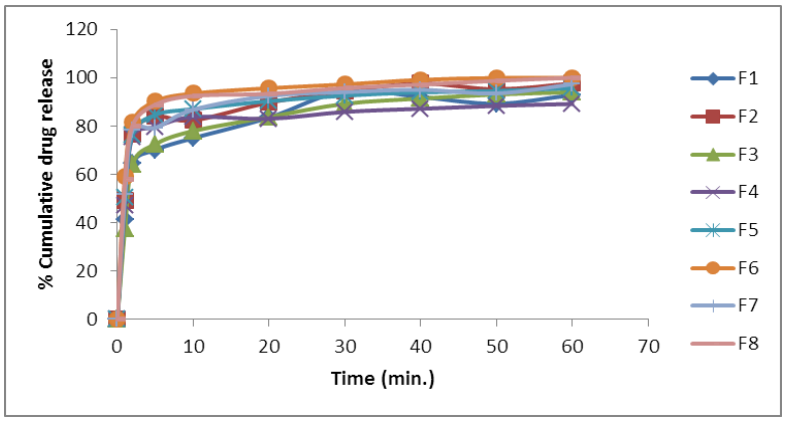

Fig. 2: Graphical representation of % cumulative drug release in 0.1 N HCl.

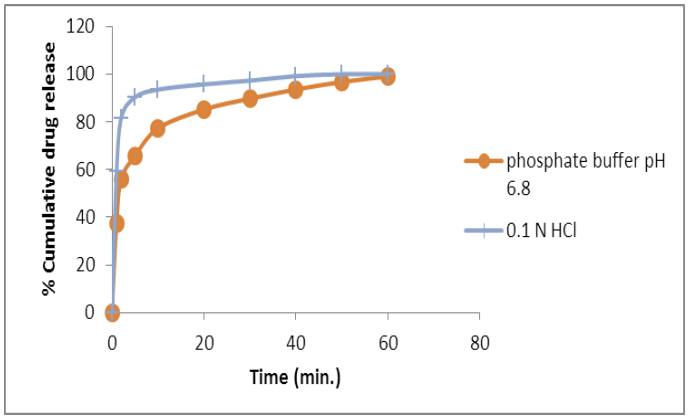

Fig. 3: In-vitro dissolution profiles of optimized batch F_6.

Table 11: Stability studies of final optimized batch F_6.

Stability condition	Sampling interval (days)	Evaluation parameters			
		% Drug content (4 mg/ 4cm^2)	Weight (mg)	Surface pH	Thickness (mm)
40°C±2°C/ 75% RH±5% RH (accelerated)	0	99.62	53	6.8	0.076
	7	99.51	50	6.8	0.074
	14	98.74	51	6.8	0.078
	21	98.69	53	6.8	0.075
	28	98.65	52	6.8	0.075
	35	98.65	52	6.8	0.076
	42	98.42	53	6.8	0.074
	49	98.37	52	6.8	0.076
	56	98.33	50	6.8	0.074
	63	98.29	52	6.8	0.075
25°C±2°C/ 60%RH± 5%RH (room temperature)	0	99.98	51	6.8	0.074
	7	99.73	53	6.8	0.076
	14	99.16	53	6.8	0.076
	21	98.99	50	6.8	0.077
	28	98.86	52	6.8	0.075
	35	98.56	50	6.8	0.076
	42	98.32	53	6.8	0.076
	49	98.27	51	6.8	0.074
	56	98.30	52	6.8	0.075
	63	98.24	52	6.8	0.075

Table 12: Evaluation parameter comparison of formulated film and marketed film.

S.No.	Evaluation parameter	Formulation comparison	
		Marketed film (4 mg dose)	Optimized film (F_6) (4 mg dose)
1.	Area	2.5×3.2 cm^2 i.e. 8cm^2	2.0×2.0 cm^2 i.e. 4cm^2
2.	Thickness	0.054 mm	0.075 mm
3.	Weight	50 mg	57 mg
4.	Percent drug content	100%	98.99%
5.	Disintegration time	20 sec	26 sec

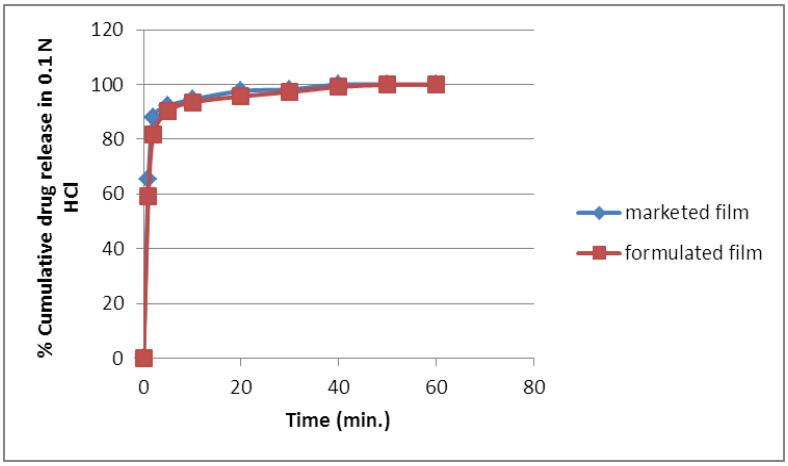

Fig. 4: % Cumulative drug release comparison graphical representation in 0.1 N HCl.

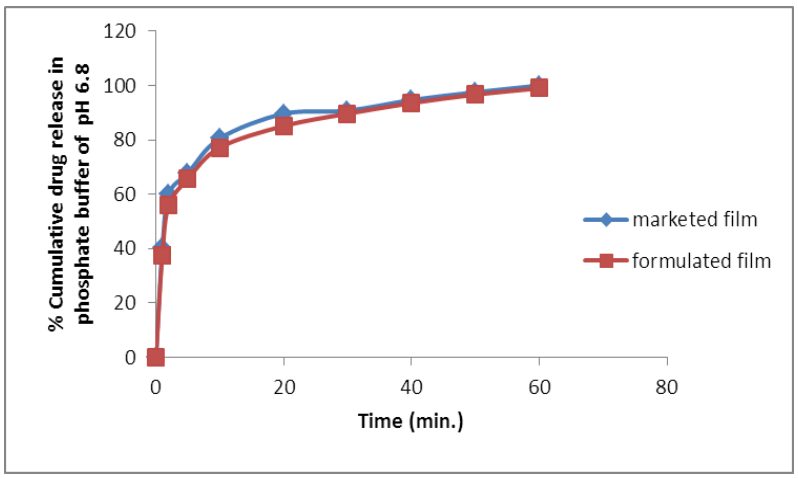

Fig. 5: % Cumulative drug release comparison graphical representation in phosphate buffer of pH 6.8.

CONCLUSION

The purpose of present research work was to explore the possibility of employing mixed-solvency concept in the formulation of a poorly water-soluble drug. Practically water-insoluble drug, ondansetron hydrochloride dihydrate was tried to be solubilized by employing the combinations of physiologically compatible solubilizers to endeavor its fast dissolving formulations.

The aqueous solubility of drug was found to be 0.0072 % w/v which was increased by using blends of solubilizers of total strength 27% w/v to get expected solubility of drug which is required for casting the film in particular dose and dimension 4mg/4cm^2.

For the development of fast dissolving film, different film forming polymers, plasticizers, superdisintegrants were tested. According to their mechanical properties and disintegration time of film, they were selected and optimized. By these ingredients, eight batches of fast dissolving film containing 4mg dose of drug per 4 cm^2 were developed and evaluated. Amongst these batches, F_6 batch showed better in-vitro dissolution profile, disintegration time and was selected for stability studies. It was found to be stable for 2 months.

After that the prepared film (F_6, 4mg) was compared with the marketed film (Emefilm, 4mg). It was found that the prepared film (F_6) showed parameters closed to the marketed film like disintegration time, thickness, % cumulative drug release etc. whereas the area of formulated film (4mg/4cm^2)was half of the area of marketed film product (4mg/8cm^2). By decreasing the area of film it was concluded that the loading of drug got increased.

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

ACKNOWLEDGEMENT

Ondansetron hydrochloride dihydrate bulk drug sample was a generous gift sample by Modern Laboratories Ltd., Indore, India.

REFERENCES

1. Rao, Raghavendra N. G., Khatoon, N., Reddy, B. M., Overview on fast dissolving oral films, International Journal of Chemistry and Pharmaceutical Sciences, 2013; 1(1): 63-75.
2. Arya, A., Chandra, A., Sharma, V., Pathak, K., Fast dissolving oral film: an innovative drug delivery system and dosage form, International Journal of Chem Tech Research, 2010; 2(1): 576-583.
3. Patil, Swapnil L., Mahaparale, Paresh R., Shivnikar, Madhavi A., Tiwari, Shradha S., Pawar, K. V., Sane, P. N., Fast dissolving oral film: an innovative drug delivery system, International Journal of Research and Reviews in Pharmacy and Applied Science, 2013; 2(3): 482-496.
4. Thakur, N., Bansal, M., Sharma, N., Yadav, G., Khare P., Overview on “a novel approach of fast dissolving films and their patents”, Advances in Biological Research, 2013; 7(2): 50-58.

5. Gupta, M. M., Patel, M. G., Kedawat, M., Enhancement of dissolution rate of rapidly dissolving oral film of meclizine hydrochloride by complexation of Meclizine hydrochloride with β-cyclodextrine, Journal of Applied Pharmaceutical Science, 2011; 1(9): 150-153.
6. Maheshwari, R. K., "Mixed-Solvency" – A novel concept for solubilization of poorly water-soluble drugs, Journal of Technology and Engineering Sciences, 2009; 1(1): 39-44.
7. Maheshwari R. K. & Rajagopalan R., Solubilization of ibuprofen by mixed solvency approach. Indian Pharm, 2009; 8: 81-4.
8. Maheshwari RK. "Mixed solvency approach" boon for solubilization of poorly water soluble drugs. Asian J Pharm, 2010; 1: 60-3.
9. Jain, R., Maheshwari, R. K., George, P., Formulation development and evaluation of controlled release tablets of lamotrigine using mixed solvency concept, Bulletin of Pharmaceutical Research, 2015; 5(1): 14-9.
10. Patel, S. K. and Maheshwari, R. K. "Formulation development and evaluation of SEDDS of poorly soluble drug made by novel application of mixed-solvency concept", International Journal of Pharmaceutical Research, 2012; 4: 51-56.
11. Shilpkar, R. and Maheshwari, R. K. "Formulation development and evaluation of injection of poorly soluble drug using mixed solvency concept", International Journal of Pharma and Bio Sciences, 2012; 3: 179-189.
12. Agarwal S. and Maheshwari, R. K. "Formulation development and evaluation of in situ nasal gel of poorly water soluble drug using mixed solvency concept," Asian Journal of Pharmaceutics, 2011; 5(3): 131-140.
13. Solanki, S. S., Soni, L. K., Maheshwari, R. K., Study on mixed solvency concept in formulation development of aqueous injection of poorly water soluble drug, Journal of Pharmaceutics, 2013; 4(2): 58-61.
14. Chaklan, N. and Maheshwari, R. K., Novel pharmaceutical application of mixed solvency for solubility enhancement of piroxicam, development of its solid dispersions and fast dissolving oral film. S.G.S.I.T.S., Indore., 2009.
15. Rajagopalan, R., Formulation and evaluation of tinidazole syrup made by mixed solvency concept, Scholars Research Library, 2012; *4*(1): 170-174.
16. Maheshwari, Y., Mishra D. K., Mahajan, S. C., Maheshwari, R. K., novel pharmaceutical application of mixed solvency in the formulation development of syrups (liquid oral solutions) of poorly water-soluble drugs, International Jornal of Pharmacy, 2013; 3(4): 753-758.

17. Karwande V. K. and Maheshwari, R. K. "Application of novel concept of mixed-solvency in the design and development of floating microspheres of furosemide, International Journal of Pharmacy and Pharmaceutical Sciences, 2013; 5: 167-175.
18. Chandna, C. and Maheshwari, R. K., Mixed solvency concept in reducing surfactant concentration of self emulsifying drug delivery system of candesartan cilexetil using D-optimal mixture design, Asian Journal of Phamaceutics, 2013; 7: 83-91.
19. Soni L. K., Solanki S. S., Maheshwari R. K., Studies on mixed solvency concept in formulation development of oral solution (syrup) of poorly water soluble drugs, Journal of harmonized research in pharmacy, 2015; 4(4): 305-315.
20. Soni L. K., Solanki S. S., Maheshwari R. K., Solubilization of poorly water soluble drug using mixed solvency approach for aqueous injection, British Journal of Pharmaceutical Research, 2014; 4(5): 549-568.
21. Maheshwari Yash, Mishra D. K, Mahajan S. C, Maheshwari Prachi, Maheshwari R. K, Jain V., Novel pharmaceutical application of mixed solvency in the formulation development of syrups (liquid oral solutions) of poorly water-soluble drugs, International Journal of Pharmacy, 2013; 3(4): 753-758.