Research Article

FORMULATION, OPTIMIZATION AND EVALUATION OF MOUTH DISSOLVING TABLETS OF PIROXICAM USING HYDROTROPIC SOLUBILIZATION TECHNIQUE

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ABSTRACT

Solubility is a most important parameter for the oral bioavailability of poorly soluble drugs. Dissolution of drug is the rate-determining step for oral absorption of the poorly water-soluble drugs, which can subsequently affect the in-vivo absorption of drugs. The delivery of such water-soluble drugs has been the subject of much research, as approximately 40% of new chemical entities are hydrophobic in nature and solubility of active pharmaceutical ingredients (API) has always been a concern for formulators. The objective of present work was to enhance the aqueous solubility of poorly soluble drug Piroxicam using hydrotropic solubilization technique and develop its mouth dissolving tablets which resulted in enhanced solubility and thus bioavailability of the drug. The present study included the formulation of mouth dissolving tablets of Piroxicam by incorporating suitable superdisintegrants, and subliming agent which were evaluated on the basis of pre and post compression parameters. Initially, physical mixtures and hydrotropic solid dispersions of Piroxicam, were prepared using selected hydrotrope i.e. sodium benzoate in different ratios. After evaluating the physical mixtures and hydrotropic solid dispersions, the particular HSD of the drug concerned, was screened out and selected for further formulation development in the form of mouth dissolving tablets. It was concluded that such novel formulation design could be extrapolated to many potential therapeutic candidates possessing poor aqueous solubilities targeting at overwhelming demand of enhanced bioavailability encompassing utmost economic relevance.

Keywords: Piroxicam; Solubility Enhancement; Hydrotropic Solubilization Technique; Hydrotropic Solid dispersion; Mouth dissolving tablets; Optimization

INTRODUCTION

The performance of orally administered dosage forms largely depends upon the inherent property of the drug candidate i.e. water solubility, which facilitates its absorption.¹ Recent researches have revealed the necessity of developing novel dosage forms together with ease of medication. ODTs are advantageous particularly for geriatric patients with whom conventional tablets and capsules are problematic in swallowing. Moreover, pediatric patients, due to immature development of muscular and nervous capabilities, also fail to ingest them. MDTs are the currently preferred dosage forms with higher patient compliance.

The oral tablets, when brought to dissolve in mouth, result in rapid absorption and quicker onsets. The drugs undergoing pregastric absorption elicit apparently increased oral bioavailability when presented as MDTs.²

Better dissolution and bioavailability rates, of poorly aqueous soluble drugs, can be attributed to the phenomenon of solid dispersion.³ An increase in aqueous solubility of the chosen drug can be brought about by the addition of another solute which is attributed as hydrotropic solubilization (Fig.1).⁴⁻⁵

MDTs induce rapid disintegration (>1 min.) of the dosage form in the oral cavity and the transformed residue is easily swallowable.⁶ Piroxicam is chemically, 4-hydroxy-2-methyl-N-(2-pyridyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. It is a selective COX-2 inhibitor used in the treatment of

rheumatoid arthritis, osteoarthritis and other joint disorders. The poor aqueous solubility of the drug made difficulty in formulation of appropriate dosage form with better absorption characteristics.⁷ Hence, the study included the formulation of MDTs of Piroxicam using hydrotropic solubilization method.

MATERIALS AND METHODS

Drug sample and carriers, used in the study were obtained from various companies of repute. Piroxicam -Ramdev Chemicals, Thane, Ascorbic acid, Sodium benzoate, Sodium acetate, Camphor, MCC & Magnesium Stearate-CDH Pvt. Ltd. Mumbai, Crospovidone & CCS-Vardha Biotech, Mumbai, Talc-Rankem and Mucin-Vivan Life Sciences, Mumbai etc.

SELECTION OF HYDROTROPE FOR POORLY AQUEOUS SOLUBLE DRUG

Equilibrium solubility determination at room temperature

The different dissolution media, consisting of distilled water, 20% solution of sodium acetate, sodium benzoate and ascorbic acid, were added with excess amounts of the drug separately and shaken (12 h at 28 $\pm$ 1 $^{\circ}$ C) mechanically, equilibrated (24 hrs) and centrifuged (5 min at 2000 rpm). The supernatant obtained in each case, was passed through whatman filter paper (No. 41). Each filtrate was suitably diluted and analyzed spectrophotometrically.⁸

DRUG-EXCIPIENT COMPATIBILITY STUDY

TLC (thin layer chromatographic) method

It involved silica gel (F₂₅₄) coated plates as stationary and ethyl acetate: toluene: butylamine (2:2:1; v/v/v) as mobile phases. Spots were evaluated at 254 nm.⁹

PREPARATION OF HSDs AND PMs

Preparation of HSDs (Hydrotropic Solid Dispersion)

Piroxicam (1.0g) was added to the aqueous medium (minimum quantity) maintained at a definite temperature (80-85⁰ C) containing sodium benzoate (2.0 g), in the dissolved state, and stirred to obtain a semisolid mass. After evaporation, such the mass was spreaded for faster drying (60-65⁰C). The pulverized mass was ground and repeatedly dried in an oven. The obtained dried powder (HSD) was sieved (# 100) and stored in an air-tight desiccator for 6 days.

PM of Piroxicam & sodium benzoate [1:4 & 1:6 (w/w)], Piroxicam & sodium acetate [1:2, 1:4 & 1:6 (w/w)] and Piroxicam & ascorbic acid [1:2, 1:4 & 1:6 (w/w)] were also prepared adopting the similar method as mentioned above.

Preparation of PM (Physical Mixtures)

Piroxicam and sodium benzoate (1:2 w/w) were accurately weighed and triturated intensely (10 min) following mechanical sifting (# 100). Piroxicam & sodium benzoate [1:4 & 1:6 (w/w)], Piroxicam & sodium acetate [1:2, 1:4 & 1:6 (w/w)] and Piroxicam & ascorbic acid [1:2, 1:4 & 1:6 (w/w)] were obtained with similar methods also (Table 1).¹⁰

EVALUATION OF HSDs AND PMs

Estimation of drug in prepared HSDs and PMs

Powdered HSD/PM containing Piroxicam (10 mg equivalent) was added with 50 ml of distilled water was added and shaken for complete dissolution. Finally, the volume was adjusted (100 ml) with distilled water. The absorbance was determined at respective wavelengths against the blank. The regression equation was used to estimate the drug content.

Dissolution rate studies of Pure drug, PMs and HSDs

The stirrer was adjusted (50 rpm) and (37⁰ ± 0.5⁰C) which was kept constant. The definite volumes (5 ml), of the withdrawn medium at fixed time intervals, were diluted suitably and analyzed. Absorbances of suitably diluted samples were determined at respective wavelengths against the blank.¹¹ The most suitable HSD was chosen for development of MDT.

PRE COMPRESSION PARAMETERS

Hydrotropic Solid Dispersion as selected in above study was examined for various parameters i.e. bulk density, tapped density, Hausner's ratio, Carr's index and angle of repose.

FORMULATION OF MOUTH DISSOLVING TABLETS OF PIROXICAM

Primarily, six batches of tablets were designed and prepared by direct compression method to screen out different superdisintegrants.

Such tablets contained solid dispersion (20mg Piroxicam equivalents), Mannitol, Saccharin, MCC, Camphor, Menthol,

Magnesium stearate and different superdisintegrants. Weight of tablets was kept constant in each batch (Table 2).

EXPERIMENTAL DESIGN

A 3² full factorial design was performed and the runs were conducted for all possible combinations. The independent variables were % of superdisintegrant (Crospovidone) (X) (2, 3.5 & 5) and % of subliming agent (Camphor) (Y) (0, 5 & 10), narrated as Factor A and B respectively (Table 3,4).

POST COMPRESSION EVALUATION PARAMETERS

Hardness, Thickness, Friability, Uniformity of weight, Disintegration time, Wetting time, Water Absorption Ratio, *In-vitro* dissolution studies, Optimization and Accelerated stability were studied as post compression parameters as per official descriptions.¹²⁻¹⁵

RESULTS AND DISCUSSION

EQUILIBRIUM SOLUBILITY DETERMINATIONS

Solubility enhancement ratios with selected hydrotropes were determined (Table 5).

TLC METHOD

The R_f values of Piroxicam (0.74-0.76), were somewhat similar, obtained with the pure drug and that in combinations with different ingredients, which confirmed the drug compatibility (fig. 2).

EVALUATION OF SOLID DISPERSIONS AND PHYSICAL MIXTURES

Determination of drug content

Drug content of each formulation was determined as summarized in Table 6.

In-vitro dissolution studies of pure drug, PMs and HSDs

Percent drug release obtained with pure drug, physical mixture and hydrotropic solid dispersion was compared and results were depicted in fig.3. Evidently, 1:6 ratio of Drug: Sodium benzoate (HSD) gave most significant release in distilled water as compared to its counterpart i.e. PM. Hence, HSD was chosen for further studies and PM was discarded.

EVALUATION PARAMETERS FOR TABLET FORMULATIONS

Pre-compression parameters for trial batches

Results obtained with (T₁-T₆) formulations showed that ranges of different pre-compression parameters were: Bulk density (0.657-0.682gm/cc), Tapped density (0.712-0.737gm/cc), Angle of Repose (25.24-27.54⁰), Carr's index (6.03-8.87%) and Hausner's ratio (1.06-1.09).

Post-compression parameters for trial batches

Results obtained with (T₁-T₆) formulations inferred were as: thickness (2.42-2.56), weight variation (passed), hardness (3.1-4.2 kg), friability (0.342-0.557%), wetting time (21-34 sec.) and water absorption ratio (65.18-80.51%).

TABLE 1: DIFFERENT RATIOS OF DRUG AND HYDROTROPE IN PM AND HSD

S. No.	Drug / hydrotrope ratio
1.	1:2 (Sodium Benzoate/ Sodium acetate/ Ascorbic acid)
2.	1:4 (Sodium Benzoate/ Sodium acetate/ Ascorbic acid)
3.	1:6 (Sodium Benzoate/ Sodium acetate/ Ascorbic acid)

TABLE 2: FORMULATION CHART FOR PRELIMINARY TRIAL BATCHES

Ingredients*	T ₁	T ₂	T ₃	T ₄	T ₅	T ₆
Hydrotropic Solid Dispersion	18.22	18.22	18.22	18.22	18.22	18.22
Sodium Starch Glycolate	2	-	4	-	4	-
Crospovidone	-	2	-	4	-	4
Camphor	-	-	-	-	5	5
Mannitol	54	54	54	54	54	54
Saccharin	8	8	8	8	8	8
MCC	114.78	114.78	112.78	112.78	107.78	107.78
Magnesium Stearate	2	2	2	2	2	2
Menthol	1	1	1	1	1	1
Total	200	200	200	200	200	200

* All quantities in mg

TABLE 3: RUNS DESIGNED IN ACTUAL AND CODED VALUES

Runs	Type	Coded values		Actual values	
		Factor A	Factor B	Factor A (%)	Factor B (%)
1.	Axial	-1	0	2	5
2.	Factorial	-1	-1	2	0
3.	Factorial	-1	1	2	10
4.	Center	0	0	3.5	5
5.	Axial	0	1	3.5	10
6.	Factorial	1	-1	5	0
7.	Axial	0	-1	3.5	0
8.	Factorial	1	1	5	10
9.	Axial	1	0	5	5

TABLE 4: FORMULATIONS BASED ON 3² FULL FACTORIAL DESIGNS

Ingredients*	F ₁	F ₂	F ₃	F ₄	F ₅	F ₆	F ₇	F ₈	F ₉
Hydrotropic Solid Dispersion	18.22	18.22	18.22	18.22	18.22	18.22	18.22	18.22	18.22
Crospovidone	4	7	10	4	7	10	4	7	10
Camphor	0	0	0	10	10	10	20	20	20
Mannitol	54	54	54	54	54	54	54	54	54
Saccharin	8	8	8	8	8	8	8	8	8
MCC	112.78	109.78	106.78	102.78	99.78	96.78	92.78	89.78	86.78
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Menthol	1	1	1	1	1	1	1	1	1
Total	200	200	200	200	200	200	200	200	200

* All quantities in mg

TABLE 5: ENHANCED SOLUBILITY DATA BY EQUILIBRIUM SOLUBILITY STUDIES

Hydrotrope solution	Conc. of hydrotrope	Solubility (mg/ml)	Solubility enhancement ratio
Distilled water	-	0.231	-
Ascorbic acid	20%	2.426	10.50
Sodium benzoate	20%	8.262	35.76
Sodium acetate	20%	3.112	13.47

TABLE 6: DRUG CONTENT IN PHYSICAL MIXTURE AND HYDROTROPIC SOLID DISPERSION

Hydrotrope	Drug hydrotrope ratio	Percent Drug Content	
		PM	HSD
Ascorbic Acid	1:2	91.34	95.18
	1:4	92.67	95.37
	1:6	93.89	96.62
Sodium Benzoate	1:2	97.34	99.78
	1:4	98.67	99.89
	1:6	98.78	99.12
Sodium Acetate	1:2	93.45	95.92
	1:4	94.66	96.73
	1:6	95.87	97.99

TABLE 7: RESULTS OF PRE-COMPRESSION PARAMETERS FOR FACTORIAL BATCHES (F₁-F₉)

S. No.	Formulation	Bulk Density (gm/cc)	Tapped Density (gm/cc)	Angle of Repose (°)	Carr's index	Hausner's Ratio
1.	F ₁	0.664	0.711	26.85	6.61	1.07
2.	F ₂	0.687	0.727	25.32	5.50	1.05
3.	F ₃	0.661	0.722	26.16	8.44	1.06
4.	F ₄	0.656	0.698	27.01	6.01	1.09
5.	F ₅	0.681	0.726	26.53	6.19	1.06
6.	F ₆	0.659	0.717	25.67	8.08	1.06
7.	F ₇	0.676	0.733	27.29	7.77	1.08
8.	F ₈	0.683	0.729	26.99	6.31	1.06
9.	F ₉	0.678	0.719	26.31	5.70	1.06

TABLE 8: RESULTS OF POST-COMPRESSION PARAMETERS FOR FACTORIAL BATCHES (F₁-F₉)

S. No.	Formulation	Thickness (mm)	Friability (%)	Hardness (kg)	Weight variation	D.T (sec)	Average wetting time (sec)	Water absorption ratio (%)
1.	F ₁	2.64	0.348	4.7	Passed	33	36	65.24
2.	F ₂	2.49	0.373	4.5	Passed	30	32	67.46
3.	F ₃	2.59	0.401	4.3	Passed	27	29	70.97
4.	F ₄	2.46	0.448	4.2	Passed	25	28	70.05
5.	F ₅	2.48	0.476	4.1	Passed	23	25	78.72
6.	F ₆	2.61	0.503	3.8	Passed	21	23	80.46
7.	F ₇	2.48	0.535	3.4	Passed	16	18	82.14
8.	F ₈	2.54	0.562	3.1	Passed	14	17	83.52
9.	F ₉	2.64	0.591	3.2	Passed	12	15	85.56

TABLE 9: MULTIPLE REGRESSION ANALYSIS FOR DEPENDENT VARIABLE

For Disintegration Time					
Polynomial equation	$Y = 23.00 - 2.33A - 8.00B + 0.50AB + 1.692E-015A^2 - 1B^2$ eq. (1)				
Correlation coefficient	0.9992				
	A	B	AB	A ²	B ²
X Coefficient	-2.33	-8.00	0.50	1.692E-015	-1
P value	0.0004	<0.0001	0.057	1	0.024
For % Friability					
Polynomial equation	$Y = 0.48 + 0.027A + 0.094B + 7.500E-004 + 6.667E-004 - 7.333E-003$ eq. (2)				
Correlation coefficient	1				
	A	B	AB	A ²	B ²
X Coefficient FM	0.027	0.094	7.500E-004	6.667E-004	-7.333E-003
P value	<0.0001	<0.0001	0.126	0.278	0.0007

TABLE 10: PREDICTED SOLUTION FOR OPTIMIZED BATCH (F₉)

Factor A (Crospovidone) (mg)	Factor B (Camphor) (mg)	D.T (sec)	Friability (%)	Desirability	Remarks
10.00	20.00	12.00	0.591	1.000	Selected

Figure 1: Counterparts of hydrotropic agent

A= Piroxicam, B= Piroxicam : Ascorbic Acid, C= Piroxicam : Sodium Acetate, D= Piroxicam : Sodium Benzoate, E= Piroxicam : Sodium Starch Glycolate, F= Piroxicam :Crospovidone

Figure 2: Photographic representation of TLC

Figure 3: Comparative release profile of Physical Mixture (PM) and Hydrotropic Solid dispersion (HSD) (A) Piroxicam and ascorbic acid, (B) Piroxicam and sodium benzoate, (C) Piroxicam and sodium acetate in distilled water

Figure 4: Comparative release profile of trial batches T₁-T₆ in pH 6.8 phosphate buffer (mean±S.D)

Figure 5: Comparative release profile of batches F₁-F₉ in (A) pH 6.8 phosphate buffer, (B) Simulated Salivary Fluid (mean±S.D)

Figure 6: Contour plot showing the influence of crospovidone and camphor on D.T

Figure 7: Contour plot showing the influence of crospovidone and camphor on friability

Figure 8: Desirability contour graph of optimized batch (F₉) of piroxicam

Figure 9: Desirability 3D graph of optimized batch (F₉) of Piroxicam

Figure 10: Comparative release profile of optimized batch (F₉) in pH 6.8 phosphate buffer and Simulated Salivary Fluid (mean±S.D)

Figure 11: Comparative release profile formulation at different time intervals (0, 30, 60 and 90 days) on stability

In-vitro dissolution studies of trial batches

In-vitro dissolution study of trial batches (in pH 6.8 phosphate buffer) revealed T₆ as the best trial batch which was further subjected to optimization study (Fig. 4).

Pre-compression parameters for factorial batches

Various inferred results were as mentioned in the table (Table 7) below.

Post-compression parameters for factorial batches

Various results were as mentioned in Table 8.

In-vitro dissolution studies of factorial batches

Prepared factorial batches were also evaluated for release characteristics in two different media i.e. pH 6.8 phosphate buffer and Simulated Salivary Fluid (Fig. 5).

OPTIMIZATION STUDY

Effect of crospovidone and camphor on D.T

It was observed from eq. (1) that A and B factors significantly affected D.T with $p < 0.05$ (negatively); while the coefficients of A, B, AB & B² also showed significant negative effects at $p \leq 0.05$ (Table 9, Fig. 6).

Effect of crospovidone and camphor on Friability

The findings revealed that A and B factors elicited significant positive effect on Friability ($p < 0.05$); indicating increased response proportionately. It was observed from eq. (2) that the coefficient of A, B and B² showed significant positive effects at $p < 0.05$ (Table 9, Fig. 7). From the above figures (Fig. 6,7), it was interpreted that disintegration time decreased from blue to orange owing to increase in camphor in the first response graph. Friability was affected by both % of camphor and Crospovidone in the second response surface graph.

The optimized study, applied to factorially designed batches (F₁-F₉), revealed the predicted solution data as depicted in Table 10, Fig. 8,9.

Hence, F₉ formulation was considered as the optimized batch. The optimized formulation (F₉) exhibited 98.88% & 99.97% release (in 30 minutes) in pH 6.8 phosphate buffer and Simulated Salivary Fluid respectively (Fig. 10).

STABILITY STUDY OF OPTIMIZED FORMULATION

As per ICH guidelines under officially prescribed conditions ($40^{\circ} \pm 2^{\circ}\text{C}/75\% \pm 5\% \text{RH}$), the performed stability studies revealed that optimized formulation was stable and thus complied with dose conformity criterion (Fig. 11).

DISCUSSION

A significantly large portion of an active drug moiety escapes gastrointestinal absorption when applied in conventional dosage forms i.e. tablet, suspension, capsules etc. This amounts to frequent administration pertaining to its low bioavailability. Conclusively, such formulation strategies could be applied to different categories of drugs bringing about their enhanced water solubility and the emerging oral dosage forms would also impart higher bioavailability to the incorporated medicament(s). The work would definitely torch newer path for future research arena.

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REFERENCES

1. Khadka P, Ro J, Hyeongmin K, Iksoo K, Jeong TK. Pharmaceutical Particle Technologies: An Approach to improve drug solubility, dissolution and bioavailability. *Asian Journal of Pharmaceutical Sciences* 2014;9;304-316.
2. Patil MR, Gujarathi NA, Rane BR. Formulation and Evaluation of mouth dissolving tablet: Review Article. *Pharma Science Monitor* 2014;5(2);7-20.
3. Luhadiya A, Agrawal S, Jain P, Dubey PK. A Review on Solid dispersion. *International Journal of Advance Research in Pharmaceutical and Biosciences* 2012;2(2);281-291.
4. Kumar VS, Raja C, Jayakumar C. A Review on solubility enhancement using hydrotropic phenomena. *International*

Journal of Pharmacy and Pharmaceutical Sciences 2014;6(6); 1-7.

5. Kapadiya N, Singhvi I, Mehta K. Hydrotropy: A Promising tool for Solubility Enhancement: A Review. *International Journal of Drug Development & Research* 2011; 3(2); 26-33.

6. Ashish P, Harsoliya MS, Pathan JK, Shruti S. A Review: Formulation of Mouth dissolving tablets. *International Journal of Pharmaceutical and Clinical Science* 2011;1(1); 1-8.

7. Singh S, Shyale SS, Bhosale G. Formulation and Evaluation of Mouth dissolving tablets of Piroxicam. *International Journal of Pharmaceutical Sciences and Nanotech* 2015;8(3);2941-2946.

8. Maheshwari RK. Analysis of bulk sample of salicylic acid by application of hydrotropic solubilization method. *Indian Journal of Pharmaceutical Sciences* 2008; 823-825.

9. Starek M, Krzek, Rotkegel P. TLC determination of Piroxicam, Tenoxicam, Celecoxib and Rofecoxib in biological material. *Journal of Analytical Chemistry* 2015; 70(3); 351-359.

10. Madan JR., Kamate VJ, Awasthi R., Dua K. Recent Patents on Drug Delivery and Formulations. 2017, doi: 10.2174/1872211311666170427100213.

11. Maheshwari RK. Quantitative spectrophotometric determination of ornidazole tablet formulation using ibuprofen

sodium as hydrotropic solubilizing agent. *Digest Journal of Nanomaterial and Biostructure* 2010;5(1); 97-100.

12. Kumar R, Patil S, Patil MB, et al. Formulation Evaluation of Mouth dissolving tablets of Fenofibrate using sublimation technique. *International Journal of Chemical Technology and Research* 2009;1(4);840-850.

13. Garg A, Gupta MM. Taste masking and formulation development & evaluation of mouth dissolving tablets of Levocetirizine dihydrochloride. *Journal of Drug Delivery & Therapeutics*. 2013;3(3); 123-130.

14. Khemariya P, Gajbhiye KR, Vaidya VD, et al. Preparation and evaluation of mouth dissolving tablets of Meloxicam. *International Journal of Drug Delivery* 2010;2;76-80.

15. Rane DR, Gulve HN, Patil VV, et al. Formulation and evaluation of fast dissolving tablet of Albendazole. *International Current Pharmaceutical Journal* 2012;1(10); 311-316.

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