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Design and Optimization of Hydrotropic Solid Dispersion of Piroxicam for Rheumatoid Arthritis

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ABSTRACT

The oral bioavailability of poorly soluble medicines is highly dependent on their solubility. In the case of weakly water-soluble medications, drug dissolution is the rate-determining stage in oral absorption, which might impact the drug's absorption in vivo. Because 40% of newly created chemical entities are hydrophobic by nature and formulators have traditionally been concerned about the solubility of active pharmaceutical ingredients (API), the delivery of such water-soluble medications has been the focus of much investigation. To increase the drug's water solubility and bioavailability, the current study aimed to manufacture hydrotropic solid dispersion for the weakly soluble medication Piroxicam for the treatment of Rheumatoid Arthritis. The Rf values of Piroxicam were found to be 0.75-0.77, confirming drug compatibility. Initially, physical mixtures and hydrotropic solid dispersions of Piroxicam, were prepared using selected hydrotrope i.e. sodium benzoate in different ratios. % drug content of PM and HSD found to be 98.69 and 99.92. The batch that was considered optimal was the one with formulation F9. In pH 6.8 phosphate buffer and Simulated Salivary Fluid, the improved formulation F9 demonstrated 98.88% and 99.97% release, respectively, within 30 minutes. The performed stability studies revealed that optimized formulation was stable and thus complied with dose conformity criterion.

Keywords: *Hydrotropic solid dispersion, physical mixture, piroxicam, rheumatoid arthritis, bioavailability*

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1. Introduction

The chronic autoimmune disease known as rheumatoid arthritis (RA) primarily affects the joints, causing discomfort, inflammation, and eventual joint disintegration. Patients' quality of life is severely reduced by the condition, and long-term care is necessary to manage symptoms and avoid joint deterioration. Because of its strong anti-inflammatory and analgesic properties, piroxicam, a non-steroidal anti-inflammatory medication (NSAID), is frequently given for the treatment of RA. Unfortunately, piroxicam's weak water solubility frequently compromises its therapeutic effectiveness, leading to inconsistent absorption and reduced bioavailability.[1-3]

The development of innovative drug delivery methods that can improve the solubility and bioavailability of poorly water-soluble medications like piroxicam is becoming more and more popular as a solution to these problems. Using hydrotropic agents to create hydrotropic solid dispersions is one method that shows promise. Compounds known as hydrotropes can greatly improve the water solubility of hydrophobic medications, promoting improved absorption and dissolution rates. Because hydrotropy does not need complexation or a major change to the drug's molecular structure, it is a more adaptable and efficient solubility augmentation strategy than other solubilization methods.[4-7]

This study investigates the creation of a hydrotropic solid dispersion of piroxicam to enhance its bioavailability and solubility. Our goal is to develop a formulation that provides consistent and improved therapeutic effects by adding hydrotropic agents into the solid dispersion matrix. This might lead to a reduction in the necessary dosage and related side effects. Important facets of this study include the choice of appropriate hydrotropic agents, adjustment of the drug-to-hydrotrope ratios and assessment of the various characteristics of the resultant solid dispersions.

With better symptom management and patient compliance, the development of a hydrotropic solid dispersion of piroxicam may mark a substantial breakthrough in the treatment of RA. This work not only shows how hydrotropic solubilization may be used more broadly to improve the bioavailability of poorly soluble medications, but it also offers a viable remedy for the solubility problems related to piroxicam.[8-10]

2. Materials and Methods

2.1 Materials

Drug sample and chemical reagents used in the formulation of liposomal gel of Atorvastatin were procured from different reputed companies.

2.2 Experimental work

2.1 Selection of Hydrotrope for Poorly Aqueous Soluble Drug

2.1.1 Equilibrium solubility determination at room temperature

Excess medication was added to each of the different dissolving media, which included distilled water, a 20% solution of sodium acetate, sodium benzoate, and ascorbic acid. The mixtures were then mechanically agitated for 12 hours at 28°±1°C, allowed to equilibrate for 24 hours, then centrifuged for 5 minutes at 2000 rpm. In every instance, the obtained supernatant was run through Whatman filter paper (No. 41). Every filtrate was diluted appropriately and subjected to spectrophotometric analysis.[11]

2.2 Drug-Excipient Compatibility Study

2.2.1 TLC (Thin Layer Chromatographic) method

It utilized ethyl acetate, toluene, and butylamine (2:2:1; v/v/v) as the mobile phases and silica gel (F254) coated plates as the stationary phases. Spots at 254 nm were assessed.[12]

2.3 Preparation of HSDs and PMs

2.3.1 Preparation of HSDs (Hydrotropic Solid Dispersion)

A minimal quantity of aqueous medium (80-85°C) containing 2.0 g of dissolved sodium benzoate was combined with 1.0 g of piroxicam and agitated to create a semisolid mass. The temperature was kept constant. The bulk was spread out for quicker drying (60–65°C) following evaporation. The ground-up material was repeatedly dried in an oven. After being sieved (#100), the dried powder (HSD) was kept for six days in an airtight refrigerator. Using the same technique as previously described, PM of piroxicam and sodium benzoate [1:4 & 1:6 (w/w)], piroxicam and sodium acetate [1:2, 1:4 & 1:6 (w/w)], and piroxicam and ascorbic acid [1:2, 1:4 & 1:6 (w/w)] were also made.

2.3.2 Preparation of PM (Physical Mixtures)

After a rigorous 10-minute trituration and mechanical sifting (#100), piroxicam and sodium benzoate (1:2 w/w) were precisely weighed. Similar techniques were used to create 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)], which are described in Table 1.[13]

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)

2.4 Evaluation of HSDs and PMs

2.4.1 Estimation of drug in prepared HSDs and PMs

5 ml of distilled water were added to powdered HSD/PM containing 10 mg equivalent of piroxicam, and the mixture was agitated to ensure full dissolution. Lastly, 100 ml of distilled water was added to correct the volume. In comparison to the blank, the absorbance at each wavelength was measured.

2.4.2 Dissolution rate studies of Pure drug, PMs and HSDs

The stirrer's speed was set to 50 rpm, and the temperature was maintained at 37 ± 0.5°C. The specific quantities (5 ml) of the removed medium were diluted appropriately and subjected to analysis at certain intervals. At each wavelength, the absorbances of samples that had been appropriately diluted were measured in comparison to a blank.[14] For the creation of MDT, the best HSD was selected.

2.4.3 Pre-Compression Parameters

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

2.4.4 Formulation of Mouth Dissolving Tablets of Piroxicam

6 batches of tablets were primarily created and manufactured using the direct compression method in order to separate out various superdisintegrants. These pills included magnesium stearate, saccharin, mannitol, MCC, menthol, camphor, solid dispersion (20 mg equivalents of Piroxicam), and several superdisintegrants. Weight of tablets was kept constant in each batch and shown in Table 2.

Table 2. Formulation Chart for Preliminary Trial Batches

Ingredients*	T1	T2	T3	T4	T5	T6
HSD	18.22	18.22	18.22	18.22	18.22	18.22
Crospovidone	-	4	2	-	-	4

Sodium Starch Glycolate	2	-	-	4	4	-
Camphor	-	-	-	-	5	5
Saccharin	8	8	8	8	8	8
Mannitol	54	54	54	54	54	54
MCC	114.78	112.78	114.78	112.78	107.78	107.78
Menthol	1	1	1	1	1	1
Magnesium Stearate	2	2	2	2	2	2
Total	200	200	200	200	200	200

2.5 Experimental Design

Runs for every conceivable combination were carried out using a 3^2 factorial design. The percentage of the subliming agent (Camphor) (Y) (0, 5 & 10) and the superdisintegrant (Crospovidone) (X) (2, 3.5 & 5) were the independent variables; they were described as Factor A and B, respectively (Table 3, 4).

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	3.5	0
3.	Factorial	-1	0	2	5
4.	Center	0	0	3.5	10
5.	Axial	0	1	2	10
6.	Factorial	0	-1	5	0
7.	Axial	0	-1	3.5	0
8.	Factorial	1	-1	5	5

9.	Axial	1	0	2	10

Table 4. Formulations Based on 3^2 Full Factorial Designs

Ingredients*	F1	F2	F3	F4	F5	F6	F7	F8	F9
HSD	18.22	18.22	18.22	18.22	18.22	18.22	18.22	18.22	18.22
Crospovidone	5	7	10	5	7	10	5	7	10
Camphor	0	0	0	10	10	10	20	20	20
Saccharin	7	7	7	7	7	7	7	7	7
Mannitol	54	54	54	54	54	54	54	54	54
MCC	112.78	109.78	106.78	102.78	99.78	96.78	92.78	89.78	86.78
Menthol	1	1	1	1	1	1	1	1	1
Magnesium Stearate	2	2	2	2	2	2	2	2	2
Total	200	200	200	200	200	200	200	200	200

* All quantities in mg

2.6 Post Compression Evaluation Parameters

Hardness, friability, thickness, uniformity of weight, wetting time, disintegration time, water absorption ratio, *in- vitro* dissolution studies, optimization and accelerated stability were studied as post compression parameters as per official descriptions.[15] Rane DR, Gulve HN, Patil VV, Thakare VM, Patil VR. Formulation and evaluation of fast dissolving tablet of albendazole. International Current Pharmaceutical Journal. 2012 Sep 5;1(10):311-6.

3. Results and Discussion

3.1 Equilibrium Solubility Determinations

Solubility enhancement ratios with selected hydrotropes were determined and summarized in Table 5.

Table 5. Enhanced Solubility Data By Equilibrium Solubility Studies

Hydrotrope solution	Conc. of hydrotrope	Solubility (mg/ml)	Solubility enhancement ratio
Distilled water	-	0.232	-
Ascorbic acid	20%	2.421	10.55
Sodium benzoate	20%	8.265	35.79
Sodium	20%	3.116	13.48

acetate			

3.2 TLC Method

When Piroxicam was taken as a pure medication and when it was combined with other substances, the Rf values (0.75-0.77) were found. This indicated that the medicine was compatible with the other ingredients, as Figure 1 illustrates.

Figure 1. Photographic representation of TLC

3.3 Evaluation of Solid Dispersions and Physical Mixtures

3.3.1 Determination of drug content

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

Table 6. Drug Content in Physical Mixture and Hydrotropic Solid Dispersion

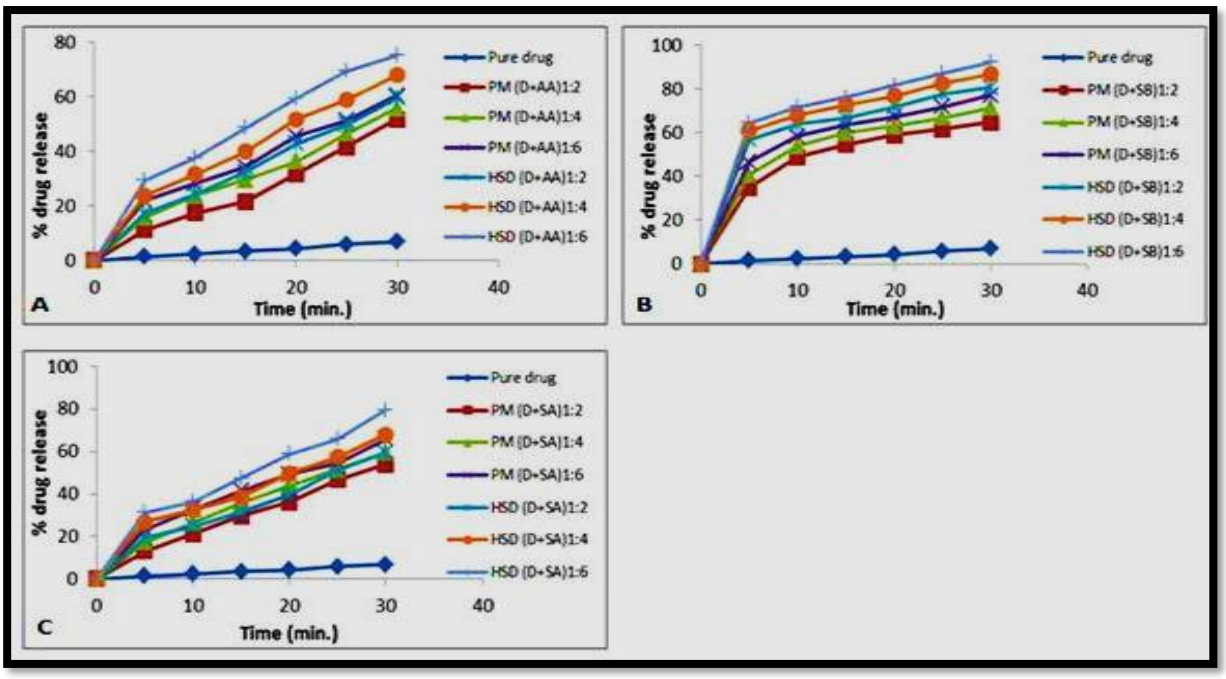
Hydrotrope	Drug hydrotrope ratio	Percent Drug Content	
		PM	HSD
Ascorbic Acid	1:2	92.45	94.98
	1:4	92.88	95.58
	1:6	93.87	96.58
Sodium Benzoate	1:2	97.38	99.75
	1:4	98.69	99.92
	1:6	98.71	99.21
	1:2	93.44	95.89

	1:4	94.62	96.71
Sodium Acetate	1:6	95.85	97.97

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

A comparison was made between the percent drug release obtained with pure drug, physical mixing, and hydrotropic solid dispersion; the outcomes are shown in figure 2. It appears that when compared to its equivalent, PM, the drug:sodium benzoate (1:6) ratio produced the greatest release in distilled water. As a result, PM was dropped and HSD was selected for more research.

Figure 2. 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

3.4 Evaluation Parameters for Tablet Formulations

3.4.1 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, shown in figure 3.

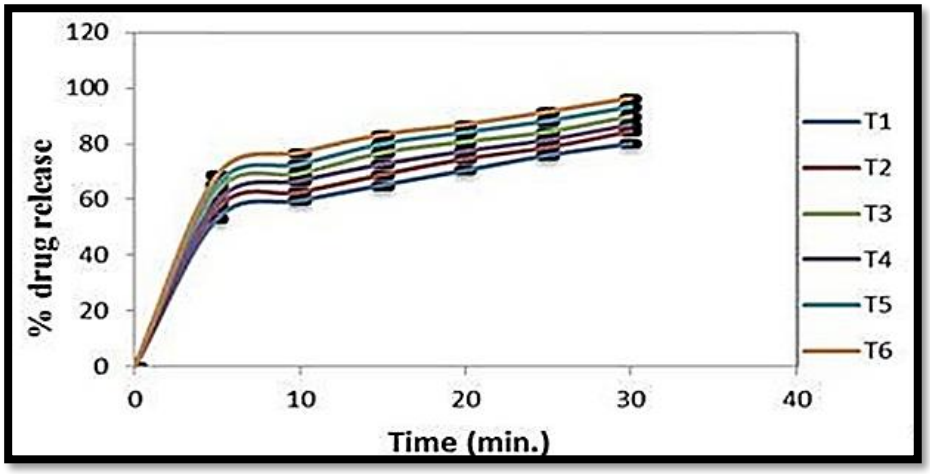


Figure 3. Comparative release profile of trial batches T1-T6 in pH 6.8 phosphate buffer (mean±S.D)

3.4.2 Pre-compression parameters for factorial batches

Various inferred results were as mentioned in the table 7.

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 (ɵ)	Carr's index	Hausner's Ratio
1.	F1	0.665	0.712	26.84	6.60	1.06
2.	F2	0.688	0.728	25.31	5.51	1.05
3.	F3	0.660	0.723	26.17	8.42	1.06
4.	F4	0.655	0.701	27.03	6.03	1.09
5.	F5	0.680	0.724	26.52	6.18	1.06
6.	F6	0.660	0.716	25.66	8.09	1.06
7.	F7	0.677	0.734	27.30	7.78	1.08
8.	F8	0.682	0.730	26.98	6.33	1.06
9.	F9	0.679	0.718	26.30	5.71	1.06

3.4.3 Post-compression parameters for factorial batches

Various results were as mentioned in Table 8.

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.	F1	2.63	0.346	4.6	Passed	34	37	65.22
2.	F2	2.48	0.371	4.3	Passed	31	33	67.43
3.	F3	2.58	0.403	4.5	Passed	26	28	70.95
4.	F4	2.47	0.447	4.1	Passed	24	27	70.07
5.	F5	2.49	0.477	4.2	Passed	22	26	78.75
6.	F6	2.62	0.501	3.7	Passed	22	24	80.44
7.	F7	2.47	0.535	3.3	Passed	17	19	82.16
8.	F8	2.53	0.561	3.2	Passed	18	17	83.54
9.	F9	2.65	0.593	3.3	Passed	13	16	85.59

3.4.4 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, shown in figure 4.

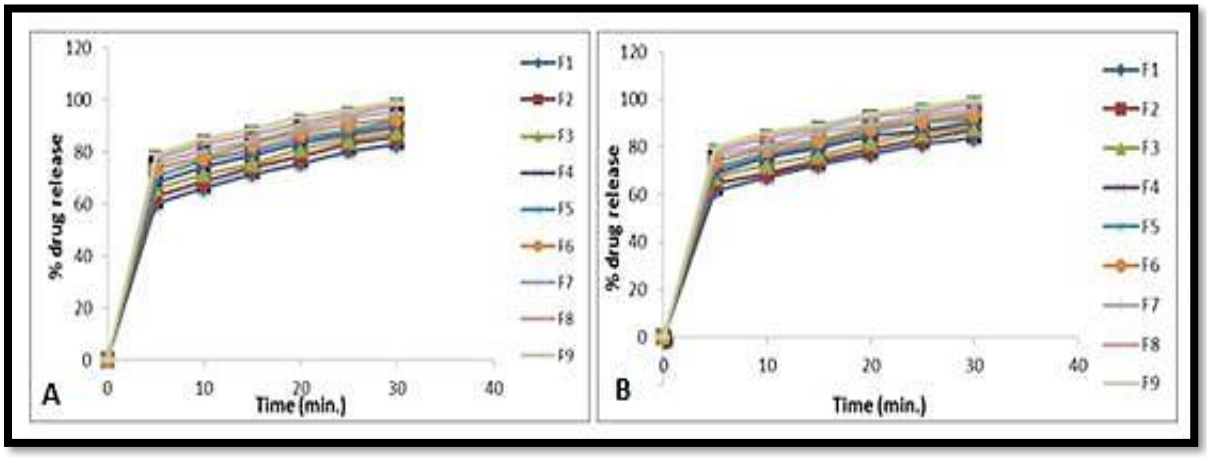


Figure 4. Comparative release profile of batches F1-F9 in (A) pH 6.8 phosphate buffer, (B) Simulated Salivary Fluid (mean±S.D)

3.5 Optimization Study

The optimized study, applied to factorially designed batches (F1- F9), revealed the predicted solution data as depicted in Table 9, Figure 5, 6.

Table 9. Predicted Solution for Optimized Batch (F9)

Factor A	Factor B	D.T (sec)	Friability	Desirability	Remarks

(Crospovidone) (mg)	(Camphor) (mg)		(%)		
10.00	20.00	13.00	0.593	1.000	Selected

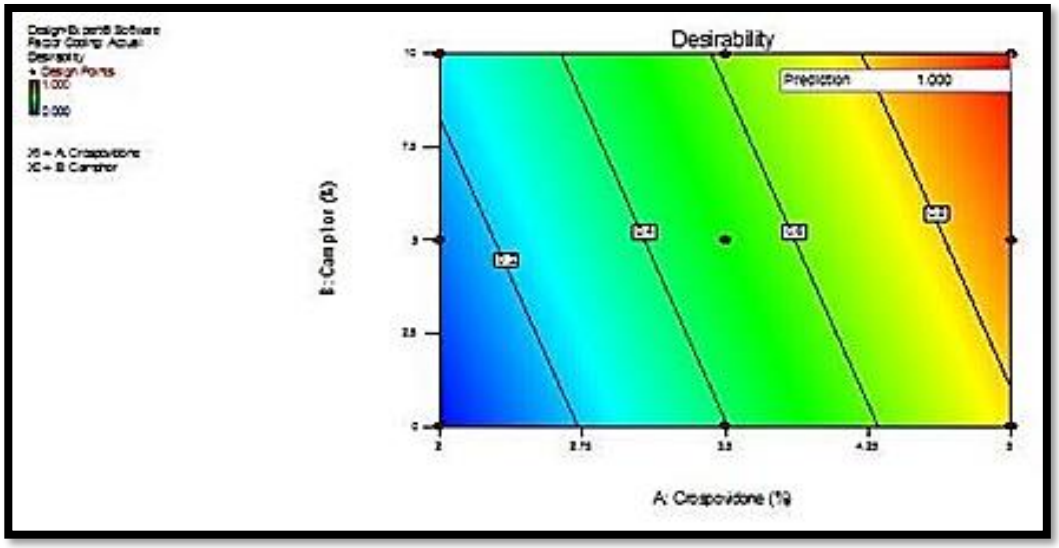


Figure 5. Desirability contour graph of optimized batch (F9) of piroxicam

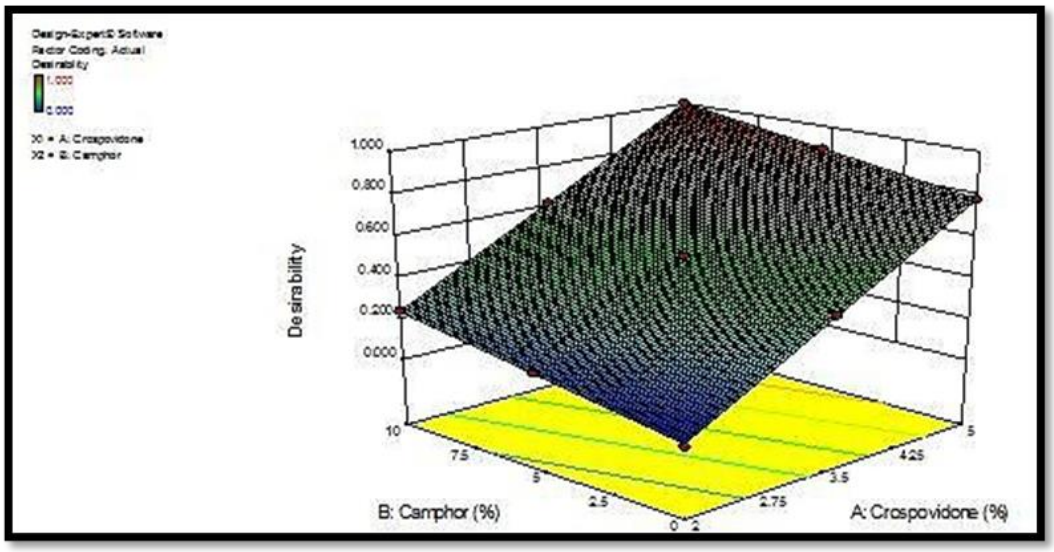


Figure 6. Contour plot showing the influence of crospovidone and camphor on friability

As a result, batch F9 formulation was regarded as optimal. Figure 7 illustrates the 98.88% and 99.97% release (in 30 minutes) that the improved formulation (F9) demonstrated in pH 6.8 phosphate buffer and Simulated Salivary Fluid, respectively.

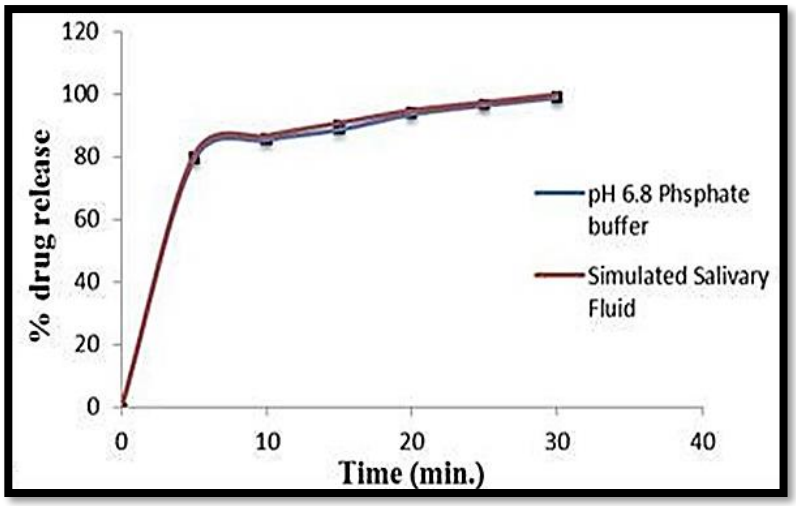


Figure 7. Comparative release profile of optimized batch (F9) in pH 6.8 phosphate buffer and Simulated Salivary Fluid (mean±S.D)

3.6 Stability Study of Optimized Formulation

The improved formulation met the dosage compliance criteria in figure 8 because stability experiments conducted under officially defined settings (40°±2°C/75%±5%RH) according to ICH guidelines were shown to be stable.

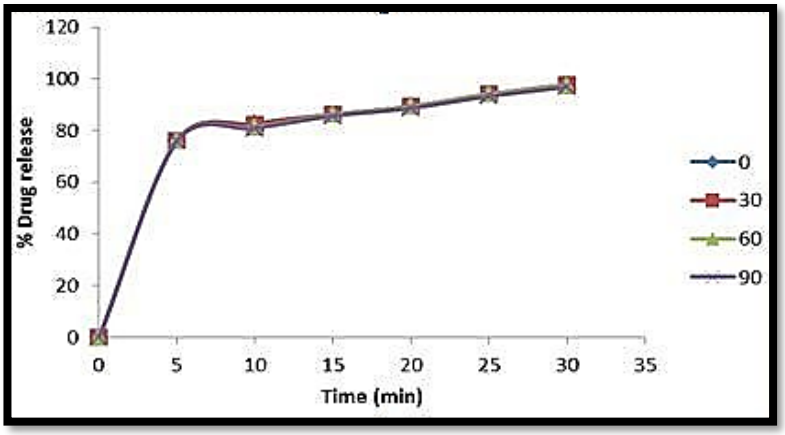


Figure 8. Comparative release profile formulation at different time intervals (0, 30, 60 and 90 days) on stability

4. Conclusion

Poorly soluble medications' oral bioavailability is strongly influenced by their solubility. The rate-determining step in oral absorption for drugs that are poorly water soluble may have an

effect on the drug's absorption in vivo when it comes to drug disintegration. Since 40% of freshly synthesized compounds are hydrophobic by nature and active pharmaceutical ingredients (API) solubility has historically worried formulators, a lot of research has gone into how to distribute these water-soluble drugs. The current study aims to produce hydrotropic solid dispersion for the poorly soluble pharmaceutical Piroxicam for the treatment of rheumatoid arthritis. This would boost the drug's water solubility and, consequently, its bioavailability. Piroxicam's Rf values were determined to be 0.75-0.77, confirming the drug's compatibility. First, varied ratios of sodium benzoate, a chosen hydrotrope, were used to create physical mixes and hydrotropic solid dispersions of piroxicam. PM and HSD were determined to have drug contents of 99.92 and 98.69%, respectively. Formulation F9-containing batch was deemed to be the best. The enhanced formulation F9 showed 98.88% and 99.97% release, respectively, after 30 minutes in pH 6.8 phosphate buffer and Simulated Salivary Fluid. The improved formulation met the dosage compliance requirement since the stability experiments were performed and found to be stable.

5. Conflict of interest

The authors have no conflict of interest.

6. Acknowledgement

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7. Reference:

1. Hasan AA, Khudhur HR, Hameed AK. Rheumatic autoimmune diseases (focus on RA): prevalence, types, causes and diagnosis. Karbala Journal of Pharmaceutical Sciences. 2022 Jan 1;1(20).
2. Thakur S, Riyaz B, Patil A, Kaur A, Kapoor B, Mishra V. Novel drug delivery systems for NSAIDs in management of rheumatoid arthritis: An overview. Biomedicine & Pharmacotherapy. 2018 Oct 1;106:1011-23.
3. Kalepu S, Nekkanti V. Improved delivery of poorly soluble compounds using nanoparticle technology: a review. Drug delivery and translational research. 2016 Jun;6:319-32.
4. Bhalani DV, Nutan B, Kumar A, Singh Chandel AK. Bioavailability enhancement techniques for poorly aqueous soluble drugs and therapeutics. Biomedicines. 2022 Aug 23;10(9):2055.
5. Bhowmik D, Harish G, Duraivel S, Kumar BP, Raghuvanshi V, Kumar KS. Solid dispersion-a approach to enhance the dissolution rate of poorly water soluble drugs. The pharma innovation. 2013 Feb 1;1(12).

6. Jain P, Goel A, Sharma S, Parmar M. Solubility enhancement techniques with special emphasis on hydrotrophy. International Journal of Pharma Professional's Research (IJPPR). 2010;1(1):34-45.
7. Sharma U, Saroha K. A Review of Hydrotropic Solubilization Techniques for Enhancing the Bioavailability of Poorly Soluble Drugs. International Journal of Toxicology. 2024 Feb;43(1):63-71.
8. Tripathi D, Chaudhary N, Sharma DK, Sahoo J. Insightful Investigative Account on Hydrotropic Solubilization Practice Utilized for Solubility Management of Poorly Dissolvable Drugs. Current Drug Therapy. 2021 Oct 1;16(5):393-408.
9. Sharma S, Sharma R, Koka SS, Darwhekar GN. A Review:"Hydrotropy" Techniques to increase the solubility of Drug. Journal of Pharmaceutical Negative Results. 2023 Feb 10:1611-8.
10. Kalyani G, Bhuvaneswari P, Hemalatha B, Padmalatha K. Hydrotropy: a promising tool for solubility enhancement. Asian Journal of Pharmacy and Technology. 2022;12(2):146-50.
11. Maheshwari RK, Bishnoi SR, Kumar D, Krishna M. Quantitative spectrophotometric determination of ornidazole tablet formulations using ibuprofen sodium as hydrotropic solubilizing agent. Digest Journal of Nanomaterials and Biostructures. 2010 Mar 1;5(1):97-100.
12. Kumar R, Patil S, Patil MB, Patil SR, Paschapur MS. Formulation evaluation of mouth dissolving tablets of fenofibrate using sublimation technique. Int J Chem Tech Res. 2009;1(4):840-50.
13. Garg A, Gupta MM. Taste masking and formulation development & evaluation of mouth dissolving tablets of levocetrizine dihydrochloride. Journal of Drug Delivery and Therapeutics. 2013 May 14;3(3):123-30.
14. Khemariya P, Gajbhiye KR, Vaidya VD, Jadon RS, Mishra S, Shukla A, Bhargava M, Singhai SK, Goswami S. Preparation and evaluation of mouth dissolving tablets of meloxicam. International Journal of Drug Delivery. 2010 Jan 1;2(1).
15. Rane DR, Gulve HN, Patil VV, Thakare VM, Patil VR. Formulation and evaluation of fast dissolving tablet of albendazole. International Current Pharmaceutical Journal. 2012 Sep 5;1(10):311-6.