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FORMULATION DEVELOPMENT AND EVALUATION OF TABLET CONTAINING SOLID DISPERSION OF POORLY SOLUBLE DRUGS

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ABSTRACT

Solid dispersion (SD) is one of the oldest and widely utilized techniques to improve the solubility of slowly dissolving drugs. A variety of pharmaceutically compatible additives using different emerging technology is used for preparing SDs. Multiple approaches were designed to prepare SDs by such as kneading, co-milling, fusion, solvent evaporation and various solvent-associated methods. The selection of appropriate preparation method and carrier is vital for producing a homogenous product affecting its stability and biological activity. Many attempts were recently carried out to improve the scalability of the applied approaches and the results were novel preparation methods such as KinetiSol, Electrospinning and Hot-melt extrusion. In the present review, drug carriers used to formulate SD were classified as small molecular weight carriers, large molecular weight named polymeric carriers and functionalized polymeric ones. Moreover, new attractive SD formulated using the newly emerged natural carriers recently joined the field of the pharmaceutical industry.

Key words: Solid dispersion, Solvent evaporation, Fusion, Co-milling, Kneading, Electrospinning, KinetiSol®.

INTRODUCTION

Oral drug delivery is the most common method due to its ease, flexibility, and cost-effectiveness. However, 40% of new chemical entities have low bioavailability due to low solubility and dissolution rates in gastrointestinal fluids. This is a limitation for Biopharmaceutical Classification System (BCS) class II drugs. Techniques like physical,

chemical modifications, and inclusion into carrier systems can boost dissolution rate and bioavailability, with the technique called SD applied to a drug generating more soluble products (1-3). Piroxicam is an NSAID used to treat the symptoms of osteoarthritis and rheumatoid arthritis. A cyclooxygenase inhibiting, non-steroidal anti-inflammatory agent [NSAID] that is well established in treating rheumatoid arthritis and osteoarthritis and used for musculoskeletal disorders, dysmenorrhea, and postoperative pain. Its long half-life enables it to be administered once daily [4-5]. The study aims to develop SNEDDS for Piroxicam, a drug with poor solubility and low oral bioavailability, to achieve immediate drug release and increased solubility. Quality by design is used to select excipients for desired quality attributes, resulting in a robust product. The investigation will involve experimental optimization techniques.

MATERIALS AND METHODS

Drugs and Chemicals

Piroxicam, Cross povidone, PEG 6000, Aspartame, Talc, and Magnesium Stearate are medications available from Balaji Drugs, Himedia Laboratories Pvt. Ltd., Mumbai, Central Drug House, New Delhi.

Preformulation studies

The drug samples were examined for appearance, color, and odor. The melting point of drug was determined using the capillary method, where a fine powder of the drug was filled in a glass capillary tube and dipped in liquid paraffin. Solubility was also determined in various buffers of different pH values, with the drug being dissolved in different beakers containing solvents and shaken for 24 hours at regular intervals (6-10).

Pre-compression evaluation of powdered blend

Key parameters evaluated during pre-compression include bulk density, tapped density, Hausner's ratio, and Carr's index, which provide insights into the flow properties and compressibility of the powder blend. Moisture content and particle size distribution also play a significant role in determining the stability and release profile of omeprazole within floating matrices (11, 12).

Formulation of Self Emulsifying Tablets containing Piroxicam

S-SEDDS preparations were blended with other excipients [Table 1] for 30 min in a laboratory scale double-cone mixer at 25 rpm. The compression weight of the tablets was set at 350 mg/tablet, and at least 300 tablets were compressed from each formulation.

Table 1: Preparation of Tablets Containing Self-Emulsifying Formulations

Formulation	F1	F2	F3	F4	F5	F6	F7	F8	F9
Solid SEDDS	104.5	105	105.5	106	106.5	107	107.5	108	108.5
Crospovidone	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5	3.5
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Tablettose 80	9	8.5	8	7.5	7	8.5	8	7.5	7
Total Weight [mg]	120	120	120	120	120	120	120	120	120

Postcompression Evaluation of Tablet Formulation

The study focuses on factors such as hardness, friability, disintegration time, and drug release kinetics. Understanding these characteristics is crucial for optimizing tablet performance and ensuring effective therapeutic outcomes. Factors like particle size distribution and moisture content also impact these evaluations. Comprehensive postcompression evaluations are essential for developing effective floating tablets that meet pharmacological standards (17-19).

RESULTS AND DISCUSSION

Preformulation Studies

Organoleptic characterization

Organoleptic characterization, melting point determination, and solubility check are essential techniques in the field of pharmaceutical sciences. These methods provide valuable information about the physical and chemical properties of drugs, which are crucial for their formulation and efficacy. Organoleptic characterization involves the sensory evaluation of a drug using our five senses – sight, smell, taste, touch, and hearing. This method helps in identifying any physical changes such as discoloration, odor, or taste alterations that may occur during storage or handling [Table 2].

Table 2: Identification and Characterization of Drug:

Characters	Observations
Colour	White to off-white
Odour	Odourless
pH	Weak base
Taste	Tasteless
Texture	Crystalline powder

Melting point determination

Melting point determination is another important technique used to assess the purity and identity of a drug. By measuring the temperature at which a solid substance melts, we can determine its melting point range and compare it with known values to confirm its identity. The Indian pharmacopeia recommended the capillary method for melting point determination, and the standard melting point of piroxicam was found to be 197°C, within the reported range of 196-198°C, indicating the drug sample's purity.

Solubility

Solubility check is also a key parameter in drug development as it determines the ability of a drug to dissolve in various solvents. This information is crucial for designing dosage forms that ensure optimal absorption and bioavailability of the drug [Table 3].

Table 3: Solubility Study of Piroxicam

Solvents	Solubility of Piroxicam [1mg/ml]
Acetone	Sparingly Soluble
Ethanol	Freely soluble
Methanol	Freely soluble
Normal Saline	Freely soluble
Water	Freely soluble

Loss on Drying

The percentage loss on drying was found to be 0.03 %.

Partition Coefficient

The study showed that major portion of drug was partitioned towards organic phase. The partition coefficient was found to be 3.15. The value is more than 1 which indicates the drug is lipophilic in nature.

Determination of Absorption Maxima and Calibration curve of Piroxicam

The absorption maxima of Piroxicam was determined by subjecting stock solution to the U.V spectrophotometer between wavelength of 200-400nm. The Aux of Piroxicam in buffer pH 6.8 was found to be 221nm, 254nm and 354 nm. The scan of Piroxicam solution in UV region [200-400] was performed to check the wave length of maximum absorption [λ_{max}]. The λ_{max} was found to be at 354 nm. Hence calibration curve of Piroxicam was constructed at 354 nm in pH 6.8 phosphate buffer by taking concentration on x-axis and absorbance on y-axis [Figure 1]. The calibration curve shown the regression coefficient of 0.999 and found to be linear in the concentration range of 2 to 10 $\mu\text{g/ml}$.

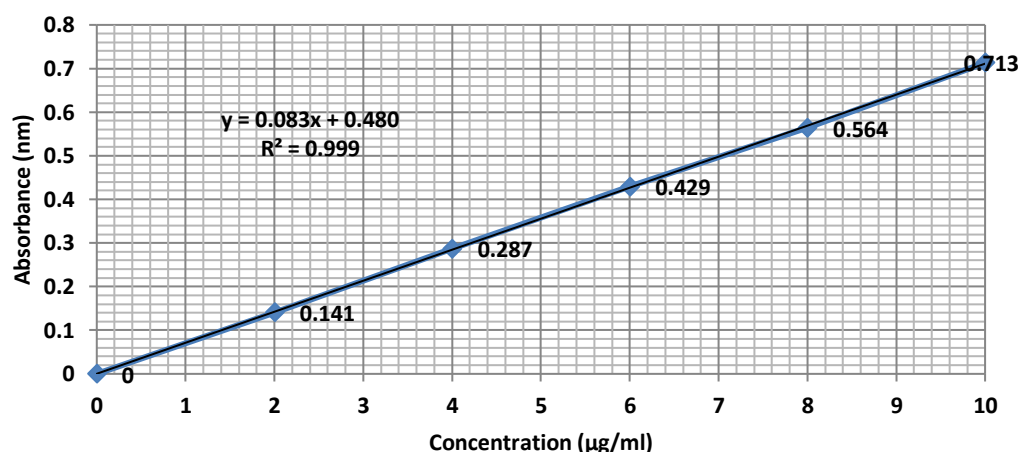


Figure 1: Calibration curve of Piroxicam [at 354 nm] in pH 6.8 phosphate buffer

Precompression Evaluation of Powder Blended Characteristics

The ideal drug release kinetics in tablet formulations are affected by parameters like particle size distribution, flow characteristics, mix consistency, and compressibility. A tight particle size distribution guarantees homogeneous mixing and inhibits segregation during compression, leading to a more consistent drug release profile. Suboptimal flow characteristics may result in heterogeneous dispersion of active compounds, leading to inconsistencies in medication release rates (Table 4).

Table 4: Physical properties of powder blends of single unit tablet formulations

Formulation	Angle of repose	Bulked Density	Compressibility index	Hausner's Ratio	Tapped Density
F1	30.6 ± 0.055	0.409 ± 0.545	19.7 ± 0.044	1.01 ± 0.856	0.501 ± 0.216
F2	31.5 ± 0.452	0.409 ± 0.056	19.9 ± 0.140	1.01 ± 0.044	0.505 ± 2.123
F3	28.5 ± 0.245	0.400 ± 0.056	19.9 ± 0.141	1.06 ± 0.056	0.509 ± 1.056

F4	30.2 ± 0.542	0.399 ± 1.556	19.2 ± 0.145	1.09 ± 0.245	0.505 ± 1.056
F5	31.8 ± 0.575	0.401 ± 0.185	19.3 ± 0.142	1.03 ± 2.056	0.500 ± 0.216
F6	30.9 ± 0.841	0.400 ± 0.855	20.1 ± 0.444	0.99 ± 0.125	0.499 ± 0.555
F7	32.15 ± 0.844	0.395 ± 0.444	19.5 ± 0.144	1.00 ± 0.111	0.501 ± 0.492
F8	30.99 ± 0.548	0.400 ± 0.736	20.1 ± 0.102	1.02 ± 0.148	0.499 ± 0.995
F9	29.24 ± 0.777	0.399	22.2 ± 0.222	0.99 ± 0.999	0.500 ± 0.501

Post compression Evaluation of Tablet Formulation

Post compression assessment is an essential procedure for assessing the quality and efficacy of tablet formulations. The evaluation encompasses factors such as hardness, friability, disintegration time, and drug release profile to ascertain the tablet's efficacy. Hardness quantifies the mechanical strength of a tablet, whereas friability assesses its propensity to fracture or chip under stress. A low friability score signifies excellent tablet integrity. The disintegration time influences the pace and degree of drug release, hence directly affecting the therapeutic efficacy of a tablet formulation. The drug release profile is the key characteristic in post-compression assessment, since it directly influences the therapeutic effectiveness of a tablet formulation (Table 5).

Table 5: Post compression Evaluation of Tablet formulation

Formulations	Drug Content Assay [%]	Disintegration Time [sec]	Hardness [kg/cm²]	Friability [%]	Thickness [mm]
F1	99.65 ± 0.076	45 ± 0.106	5.98 ± 0.056	0.32 ± 0.666	3.005 ± 0.46
F2	99.95 ± 0.056	47 ± 0.486	6.15 ± 0.156	0.32 ± 0.106	2.094 ± 0.116
F3	99.99 ± 0.996	49 ± 0.886	6.01 ± 0.106	0.33 ± 0.666	2.995 ± 0.416
F4	99.94 ± 0.006	50 ± 0.926	5.98 ± 0.046	0.33 ± 0.126	3.002 ± 0.106
F5	99.85 ± 0.106	47 ± 0.916	6.01 ± 0.116	0.29 ± 0.116	3.053 ± 0.456
F6	99.41 ± 0.415	48 ± 0.481	6.06 ± 0.441	0.3 ± 0.451	3.011 ± 0.458
F7	97.54 ± 0.455	48 ± 0.451	6.11 ± 0.449	0.31 ± 0.451	2.999 ± 0.125
F8	99.04 ± 0.145	49 ± 0.414	6.00 ± 0.441	0.28 ± 0.415	2.999 ± 0.145
F9	98.89 ± 0.411	50 ± 0.422	6.00 ± 0.499	0.29 ± 0.444	3.001 ± 0.415

In vitro Drug Release Study

All the formulations batches were subjected to in-vitro dissolution studies using pH 6.8 phosphate buffer. The present drug release of all formulation was determined in pH 6.8 phosphate buffer at the interval of 2,4,8,6,10,15,20 minutes. Data of present drug release in phosphate buffer is shown in table 6.8 and plot for dissolution profile of all the formulations [Table 6; Figure 2]. The comparative effect of the different superdisintegrants on the release profile of drug piroxicam from the nine different formulations showed that increase in the concentration of superdisintegrant increased disintegration time of the tablets. Among all the different superdisintegrants used, Tablettose 80 found high drug release profile of piroxicam. Among all formulations, F7 formulation containing highest concentration of superdisintegrant and sublimating agent showed sustained drug release till 20 minutes compared to other formulations.

Table 12: In vitro drug release studies

Time Slots [minutes]	F1	F2	F3	F4	F5	F6	F7	F8	F9
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00
2	11.24 ± 0.700	5.54 ± 0.606	51.26 ± 0.325	63.55 ± 0.777	29.25 ± 0.726	5.54 ± 0.766	36.26 ± 0.356	32.41 ± 1.756	9.24 ± 0.714
4	29.25 ± 0.246	11.65 ± 0.126	69.35 ± 0.255	71.26 ± 0.245	39.25 ± 0.756	11.65 ± 0.756	46.21 ± 0.116	40.25 ± 0.756	30.25 ± 0.246
6	39.25 ± 0.212	29.25 ± 0.246	78.25 ± 0.222	83.26 ± 0.333	49.25 ± 0.216	29.25 ± 0.512	56.95 ± 0.116	51.26 ± 0.006	43.25 ± 0.012
8	49.25 ± 0.756	39.25 ± 0.216	86.14 ± 0.106	98.12 ± 0.112	55.26 ± 0.756	35.25 ± 0.756	63.55 ± 0.756	59.35 ± 0.756	50.25 ± 0.756
10	55.26 ± 0.756	49.25 ± 0.226	99.65 ± 0.756	-	63.25 ± 0.756	41.25 ± 0.416	70.26 ± 0.446	68.25 ± 0.756	63.25 ± 0.700
12	63.25 ± 0.545	55.26 ± 0.176	-	-	71.25 ± 0.246	51.26 ± 0.226	80.26 ± 0.126	76.14 ± 0.256	74.25 ± 0.525
15	70.25 ± 0.006	63.25 ± 0.700	-	-	87.55 ± 0.246	59.35 ± 0.745	95.12 ± 0.125	85.65 ± 0.516	89.14 ± 0.106
20	89.55 ± 0.126	74.25 ± 0.525	-	-	92.25 ± 0.246	68.25 ± 0.711	99.91 ± 0.786	96.21 ± 0.745	93.05 ± 0.756

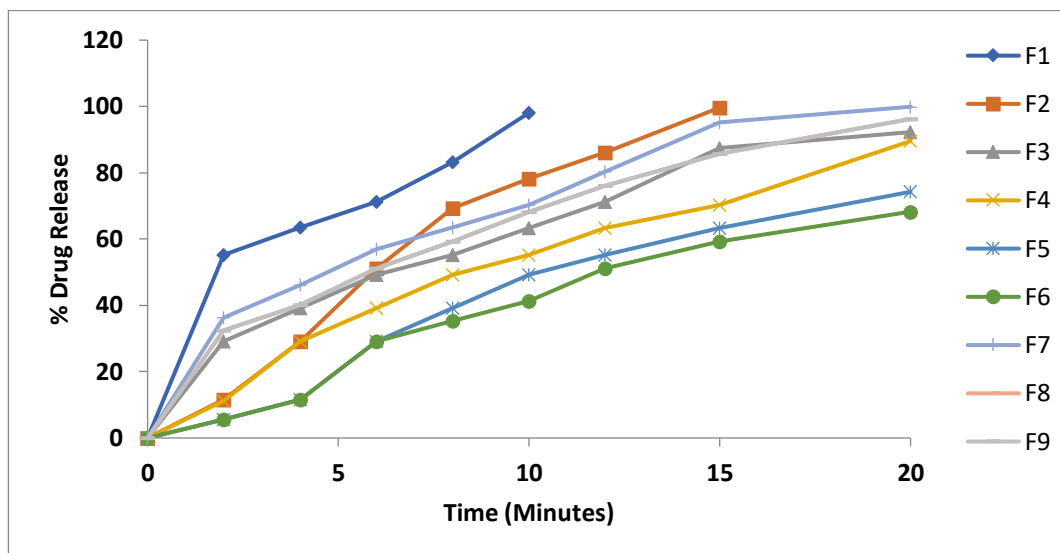


Figure 2: In vitro drug release studies

Stability Studies

Stability Study of Optimized Batch [F7] is shown in Table 13. As per the data, it was concluded that tablet dosage form was stable enough till 6 months under the accelerated conditions as per the ICH.

Table 7: Stability Study of Optimized Batch [F7] under accelerated Conditions as per ICH guideline

Test parameters	Specifications	Initials	1 st Month	3 rd Month	6 th Month
Description	Buff coloured coated spherical pellets	Buff coloured spherical Tablets	No change	No change	No change
Moisture content	NMT 2.5	1.35	1.92	1.35	1.29
Assay [Drug Content]	NLT 90% and NMT 110% of label claim	98.93 ±1.23	98.56 ±1.73	99.56 ±0.73	98.06 ±1.33

CONCLUSIONS

The study conducted a preformulation study of Piroxicam drug, which is crucial for formulation planning and identifying logical paths in liquid and solid dosage form technology. The results showed satisfactory results in characterization, including organoleptic properties, calibration curve, and partition coefficient. The Indian pharmacopeia recommends the capillary method for melting point determination, with Piroxicam's standard melting point of 197°C. The study also found that the majority of the drug is partitioned towards the organic phase, indicating lipophilic nature. The study also highlighted the importance of evaluating powder blended characteristics for consistent and reliable matrix tablet formulations. The product had a Carr Index of 11.2 to 15.7 and a Hausner grain ratio of 1.02 - 1.18. The study also examined the effect of three different superdisintegrants on the release profile of Piroxicam, finding that the maximum release was achieved with the natural polymer. The study concluded that Formulation batches F7 were the best, indicating further evaluation of their stability among other formulations.

Conflict of Interest

None

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