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Research Article

Effects of Granulating Agents in the Solubility Enhancement of Low Water Soluble Drug

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Abstract:
It is widely recognized that, according to the Biopharmaceutics Classification System (BCS), Class II drugs are defined by low aqueous solubility and high permeability. As a result, developing formulations for these drugs is particularly complex and challenging. Incomplete or inconsistent drug release can lead to reduced absorption and poor bioavailability. Therefore, there is a strong need to develop innovative strategies for Class II drugs to enhance their bioavailability and improve drug release.
The limited aqueous solubility of an active pharmaceutical ingredient (API) directly impacts both drug release and its permeability across biological membranes, thereby affecting overall bioavailability. Consequently, improving the solubility of these drugs through the use of suitable excipients or solubility-enhancing agents is essential to increase their dissolution in biological media.
This study focused on solubility enhancement approaches for the active molecule Celecoxib. Various types of granulating agents were employed in tablet formulation, and their physicochemical properties were systematically evaluated.
Keywords: Granulating Agents, Solubility, Bioavailability, Drug Release

1.0 Introduction

To enhance drug solubilization, several techniques are available in pharmaceutical science, such as drug micronization, salt formation, and the use of suitable surfactants or co-solvents[1]. To achieve the full therapeutic benefit of a drug, the active moiety must be completely released from its dosage form at the site of absorption. The quality of any dosage form is primarily determined by its drug release characteristics in biological fluids and its bioavailability[2-3].

Bioavailability is defined as the fraction of an administered drug that reaches the systemic circulation in its active form after crossing biological membranes. In other words, it refers to both the rate and extent to which the active moiety enters the bloodstream from a pharmaceutical formulation[4-5]. Injectable dosage forms typically exhibit 100% bioavailability. However, despite this advantage, injectable formulations are often less preferred due to factors such as patient discomfort, painful administration, and stability concerns during storage. From the patient's perspective, the oral route of administration is generally the most preferred and convenient option[6]. Nevertheless, oral formulations have certain limitations related to the

physicochemical properties of the drug, the type of dosage form, and patient-related factors.

The quality attributes of the finished product are influenced by various formulation and manufacturing parameters. From a formulation standpoint, the characteristics of the active pharmaceutical ingredient (API)—including particle size, solubility, crystallinity, flowability, compressibility, compatibility with excipients, and stability within the dosage form—play a crucial role. Additionally, the type and quantity of excipients used significantly affect the performance of the final dosage form[7].

Manufacturing process parameters also have a substantial impact. Factors such as the type of granulation method, the quantity and timing of granulating agent addition, drying time, residual moisture content of dried granules, lubrication time, compression force, and resulting tablet hardness all influence the overall characteristics and quality of the finished dosage form[8].

2.0 MATERIALS AND METHODS

Celecoxib was received as gift sample from M/s Ind-Swift limited and other excipients received from different vendors as gift sample.

2.1 Standard Curve

Multiple strength of Celecoxib i.e. 5µg, 10µg, 15µg, 20µg and 25µg per ml were prepared after dilution of the Standard solution of Celecoxib with the required quantity of 0.1N HCl.

Testing vials were scanned against the 0.1N HCl as a blank, in spectroscopy at the λ of 254 nm.

2.2 Manufacturing of Tablets

According to Table 1.0 composition, Celecoxib, Pharmatose, and Avicel were combined and passed through mesh number 20. Binder agent was prepared using purified water. This binder solution was used for granulation of dry mix powder. Wet mass was dried at 60°C for 35 minutes. Dried granules were further sized using suitable sieve. Dried granules were lubricated using lubricants and compressed into the tablet form.

2.3 Evaluation of Tablets

Tablets were crushed into the form of fine powder. This powder form was dissolved in the solvent and further diluted with the dissolution media. This solution was analyzed using UV visible spectroscopy at the wavelength of 254 nm. Tablet Hardness, Friability and Disintegration time was analyzed by using respective equipments. Drug dissolution was analyzed using Dissolution test apparatus using 0.1N HCl as dissolution media. Sample collected at different time periods were treated with sufficient dilution media and analyzed using UV-Visible spectroscopy at the wavelength of 254 nm.

Table 1.0 Formulation composition

	Composition						
Component	**E1 (Qty/tab.)**	**E2 (Qty/tab.)**	**E3 (Qty/tab.)**	**E4 (Qty/tab.)**	**E5 (Qty/tab.)**	**E6 (Qty/tab.)**	**E7 (Qty/tab.)**
Celecoxib	100.00 mg	100.00 mg	100.00 mg	100.00 mg	100.00 mg	100.00 mg	100.00 mg
Gum Arabic	**4.00 mg**	0.00	0.00	0.00	0.00	0.00	0.00
Pharma sugar	0.00	**4.00 mg**	0.00	0.00	0.00	0.00	0.00
Plasdone	0.00	0.00	**4.00 mg**	0.00	0.00	0.00	0.00
Carbowax	0.00	0.00	0.00	**4.00 mg**	0.00	0.00	0.00
Metolose	0.00	0.00	0.00	0.00	**4.00 mg**	0.00	0.00
Starch Paste	0.00	0.00	0.00	0.00	0.00	**4.00 mg**	0.00
Cravogel	0.00	0.00	0.00	0.00	0.00	0.00	**4.00 mg**
Avicel	43.00 mg	43.00 mg	43.00 mg	43.00 mg	43.00 mg	43.00 mg	43.00 mg
Talcum	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg	2.00 mg
Compritol	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg	3.00 mg
Pharmatose up to	200.00 mg	200.00 mg	200.00 mg	200.00 mg	200.00 mg	200.00 mg	200.00 mg

3.0 RESULTS AND DISCUSSION

3.1 Calibration Curve

The observed results are mentioned in Table 2.0 & Fig. 1.0.

Table 2.0 Calibration curve of Celecoxib

Concentration	Absorbance
5 µg/ml	**0.151**
10 µg/ml	**0.295**
15 µg/ml	**0.427**
20 µg/ml	**0.594**
25 µg/ml	**0.745**

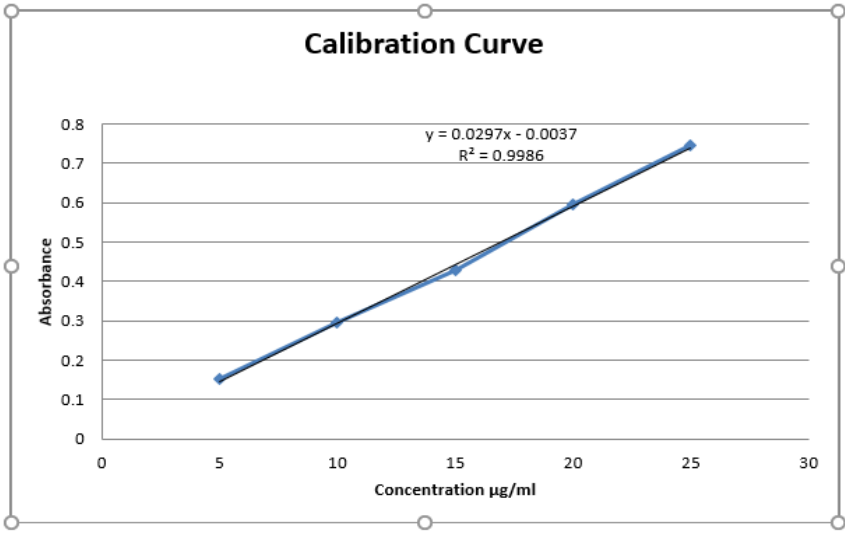

Fig. 1.0: Calibration Curve of Celecoxib

As per the results this method follows the Beer's law. Hence this method can be utilized for the *in-vitro* drug dissolution study.

3.2 Evaluation of Tablets

Table 3.0 Physical Parameters of Tablets

Formulation	Drug Content	Hardness	Friability	DT
E1	100.8	4.0-6.0 Kp	0.45%	2.7 min
E2	100.3	7.0-8.0 Kp	0.76%	0.7 min
E3	100.2	4.3-5.0 Kp	0.53%	2.0 min
E4	99.7	11-12 Kp	0.20%	18.0 min
E5	99.4	11-12 Kp	0.18%	16.0 min
E6	100.1	4.5-5.5 Kp	0.45%	1.1 min
E7	99.6	4.5-5.5 Kp	0.10%	1.0 min

Physical parameters of the different formulations are as per the Table 3.0. For different formulations observed tablet harness was satisfactory i.e. 4.0 Kp to 12 Kp. Additionally, the tablets friability was also within the Pharmacopoeial acceptance criteria.

Disintegration time of the all formulations was satisfactory except the formulation E4 & E5. In those formulations DT was observed to be more than 15 min. Assay of the drug for all formulations were also well within the acceptance criteria.

Table 4.0 Drug Release of Tablets

Time	% Release (X + SD)						
	E1	E2	E3	E4	E5	E6	E7
5 min	28.65% ± 1.2	44.41% ± 1.30	32.10% ± 1.50	5.95% ± 0.95	15.81% ± 0.95	30.61% ± 1.30	23.91% ± 1.10
10 min	48.31% ± 1.40	49.10% ± 1.20	39.90% ± 1.20	10.71% ± 1.10	27.05% ± 1.40	43.21% ± 1.10	31.70% ± 1.20
20 min	61.20% ± 1.50	57.10% ± 1.20	48.81% ± 1.10	26.91% ± 0.93	43.01% ± 1.10	59.21% ± 1.40	44.30% ± 1.20
30 min	69.78% ± 1.10	61.80% ± 1.40	54.90% ± 0.93	38.80% ± 1.40	49.91% ± 1.30	69.81% ± 0.95	54.41% ± 1.40
40 min	78.50% ± 0.95	66.90% ± 1.10	60.80% ± 1.40	41.32% ± 1.10	54.10% ± 1.10	70.65% ± 0.93	61.51% ± 0.95
50 min	86.20% ± 1.60	71.70% ± 0.94	65.85% ± 1.20	44.75% ± 1.30	60.28% ± 0.96	74.65% ± 1.30	65.20% ± 1.10
60 min	91.40% ± 1.40	78.30% ± 1.30	71.80% ± 1.10	49.48% ± 1.10	64.61% ± 1.10	85.65% ± 1.20	70.81% ± 1.40

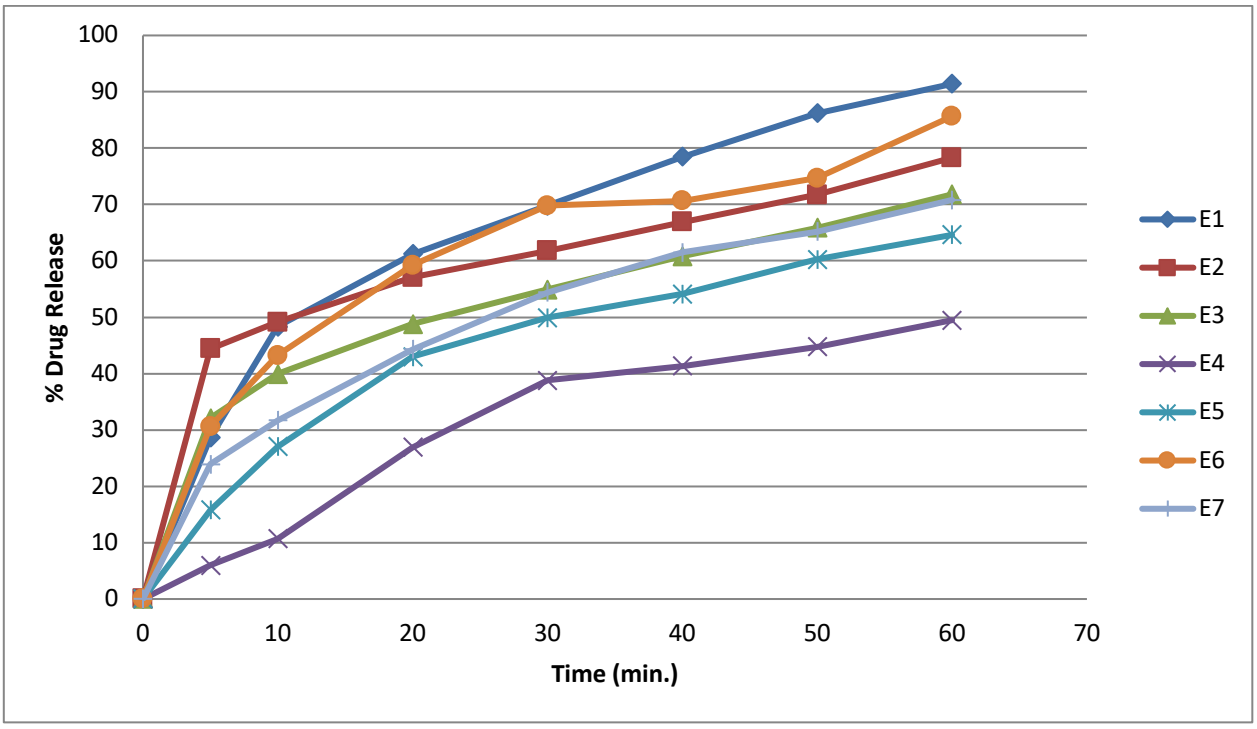

Fig. 2.0: Percentage Drug Release of Tablets

Among all formulation drug dissolution profile (Table 4.0; Fig. 2.0) for the formulation E1 was satisfactory. In rest of the formulations incomplete drug release was observed.

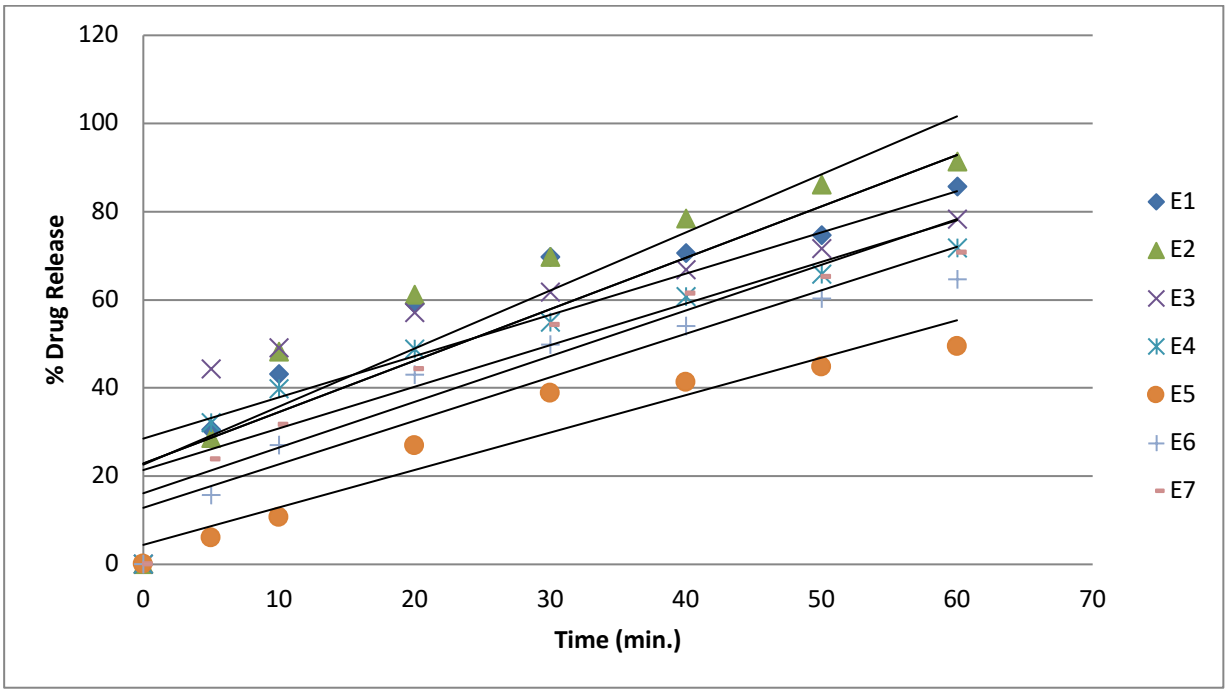

Fig. 3.0: Zero order drug release kinetics

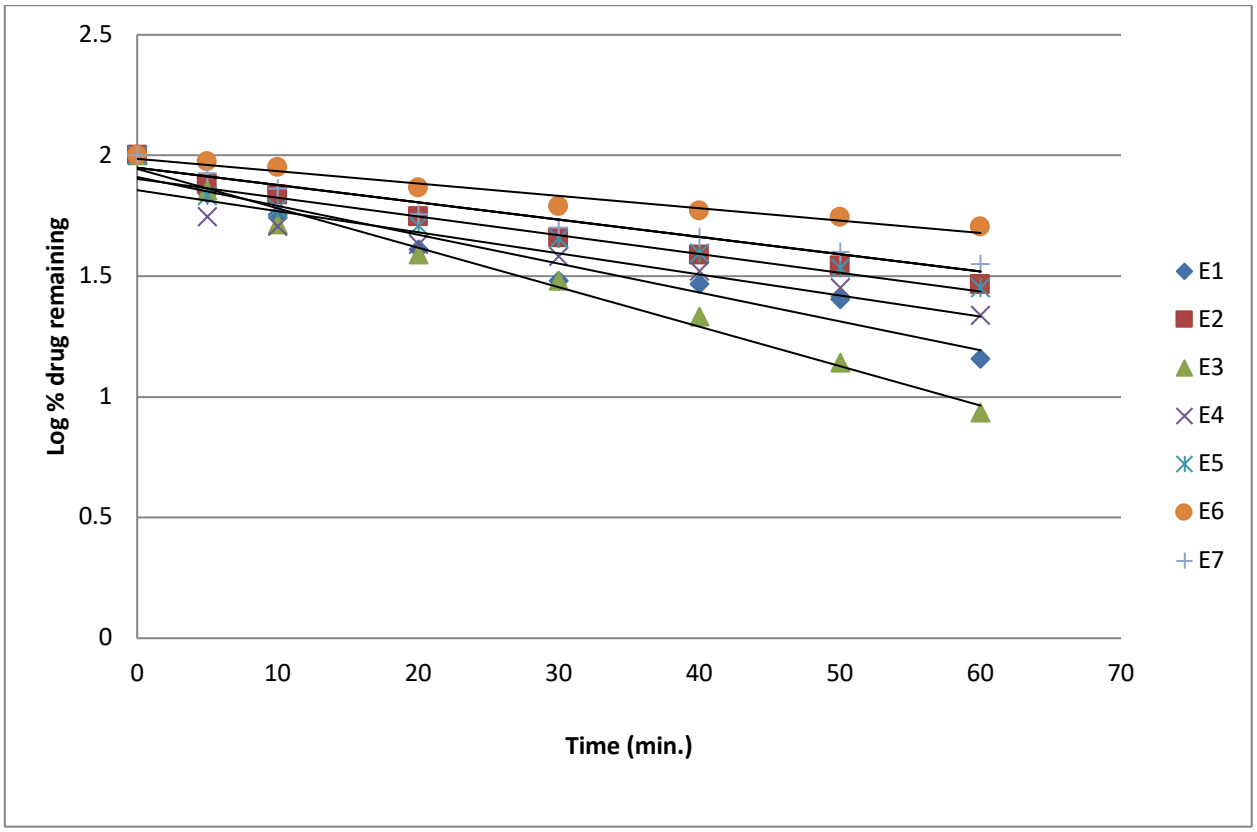

Fig. 4.0: First order drug release kinetics

Table 5.0 Values of (r) according to Zero order and First Order Kinetics

Formulation	Zero Order R^2	First Order R^2
E1	0.853	0.986
E2	0.701	0.885
E3	0.815	0.937
E4	0.927	0.956
E5	0.887	0.957
E6	0.818	0.942
E7	0.882	0.968

Release kinetics and their R^2 values are mentioned in Fig. 3 & 4 and Table 5.0. As per the Results Drug release for all formulations are following first order kinetics.

4.0 CONCLUSION

Solubility of the drug is characterized by its dissolution behavior in the media. In this study it was observed that the formulation manufactured using the granulation agent Gum Arabic has satisfactory and complete drug release when compared to other drug release. Therefore, it can be concluded that the solubility of the drug increases to a satisfactory level in the presence of Gum Arabic, starch, and pharma sugar as compared to others.

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