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Research Article

Application of Eudragit RS 30D as a Potential Drug Release Retardant of Acetaminophen and Caffeine for Prolonged Duration of Comfort

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The objective of the study is to formulate an extended release matrix tablet dosage form containing acetaminophen and caffeine by applying polymer technology which will relieve all kinds of pain for about 12 hours. Considering the fact that there is no such formulation available in the pharmaceutical market, it is expected that this drug could be an effective introduction. Hydrophobic polymers have a great application in pharmaceutical sciences as they retard the release of water-soluble drugs and give prolonged effect. *Eudragit RS 30D* was used to prepare 3 formulations (EF1, EF2, and EF3) containing varying concentrations of polymer, through the wet granulation method. Each tablet contained 1000 mg of acetaminophen and 130 mg of caffeine including other suitable excipients. All pharmacopeial and nonpharmacopeial tests were conducted to determine the quality of dosage form and to identify optimized formulation among EF1-EF3. Dissolution was conducted on similar gastric conditions through which different kinetic models were applied using DDSolver. For 12 hrs of dissolution, caffeine was released from EF1, EF2, and EF3 with the percentage release in the range from 99.85% to 100.65%, 99.32% to 100.28%, and 98.09% to 100.77%, respectively. For acetaminophen, the percent release was from 99.81% to 100.91%, 100.24% to 100.91%, and 86.81% to 95.73% for EF1-EF3, respectively. Results concluded that EF2 is the most optimized drug having all physicochemical quality control tests within the specified limits. On applying different models like zero-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas upon use, it is concluded that the formulation follows Korsmeyer-Peppas as it was the best-fitted model with the r^2 value closest to 0.999. EF2 is considered as a potential drug to be manufactured that will give prolonged relief against pain and will decrease compliance issues related to dosing frequency.

1. Introduction

Modified oral drug delivery systems are considered as a new approach towards the development of drugs [1]. Physicochemical parameters affecting the performance of a drug are being studied extensively; pharmaceutical companies are focusing on the modification and development of available drugs in the market such that they will have better safety and efficacy that will lead to increased patient compliance due to low dosing and improved efficacy [2]. Controlled release formulations are prepared with the intention to control the release of the drug over the period of time with the maintenance of effective drug concentration within the blood or plasma, for which different mathematical models are applied for the prediction of the release kinetics of the controlled release dosage form [3, 4].

Eudragit® RS 30D is a copolymer of *ethyl acrylate*, *methyl meth acrylate*, and a low content of *methacrylic acid ester* with *quaternary ammonium groups* [4–6]. It is *a hydrophobic polymer* used to control the release rate of the drug; structural and physicochemical characteristics of polymers play an important role while selecting them for a particular chemical and release time and pattern [5, 7]. Eudragit RS 30D is extensively used for the formulation of sustained release

Table 1: Formula for the formulation of acetaminophen and caffeine using Eudragit RS 30D.

Formulation	Acetaminophen (mg)	Caffeine (mg)	Eudragit RS 30D (mg)	Magnesium stearate (mg)	Lactose (mg)	Talcum (mg)
EF1	1000	130	130	13	56	26
EF2	1000	130	170	13	56	26
EF3	1000	130	200	13	56	26

products [6]. The current literature survey suggests that this polymer has been used in the formulation of pellets, coating of pellets, osmotically driven pellets, etc. [5, 8].

Eudragit RS 30D is available as a latex-like liquid dispersion and it is a *methacrylic ester polymer* [9, 10]. The possible mechanism of release of the drug in such a type of tablet is diffusion [10, 11]. Solute transport from nondegradable polymeric systems is mainly considered as diffusion driven [5]. The hydrophobic system is not suitable for poorly soluble drugs because their release rate is slow due to low concentration gradient [3].

Acetaminophen has been a choice of *analgesic and antipyretic effect* for over one hundred and twenty years. It has been prescribed by practitioners extensively and it is also an over-the-counter drug [12]. As compared to other *nonsteroidal anti-inflammatory drugs* (NSAIDs) or *cyclooxygenase* (COX-2) inhibitors, it is the feeblest analgesic and it is highly preferred due to its increased tolerance level compared to other analgesics [13, 14]. *Caffeine* is a compound to which most people in the world are exposed to in different ways [15]. The activity of adenosine causes a reduction in pain which is the main mechanism of action of caffeine [16]. *Acetaminophen and caffeine* in combination are considered to be more effective than acetaminophen alone for the treatment of different pains including headache, dental pain, and postpartum pain [13, 17].

The formulation is novel with respect to the application of polymer technology in order to *retard the release of the drug* to obtain the *prolonged duration of comfort*, and no such application of polymer technology has been done. The idea behind the development of this *extended release* acetaminophen and caffeine tablets is to treat several acute and chronic conditions like fever, headache, osteoarthritis, and postoperative pain with increased patient *compliance* and *prolonged duration of action* with fewer chances of *dose skipping*. This system is designed with an intention that at the regular interval, a required amount of drug will be delivered for action and therapeutic concentration will be maintained for a longer period of time.

2. Materials and Methods

Caffeine and acetaminophen were gifted by Tabros Pharmaceuticals Pakistan; magnesium stearate (Sigma-Aldrich, Germany), lactose DC (Sigma-Aldrich, Germany), Eudragit RS 30D (Evonik Industries, Germany), talc (Sigma-Aldrich, Germany), potassium hydroxide (KOH) (Daejung, Korea), sodium hydroxide (NaOH) (Daejung, Korea), hydrochloric acid (HCl), monobasic potassium (Riedel-de Haën, Germany) were purchased accordingly.

All other apparatus and reagents were commercially purchased (analytical grade): the dissolution apparatus (ERWEKA, Germany), spectrophotometer (Shimadzu Model UV-1800 240 V, Japan), single punch machine, granulator and mill (TP-SD-11) (KORSCH ERWEKA, Germany), climatic chamber (model KBF 720 for 40C°/75RH and model AH-36NL for 30°C/65RH).

2.1. Formulation Development. Formulations were made by wet granulation and direct compression techniques using Eudragit RS 30D, magnesium stearate lactose, and talcum in the different compositions given in Table 1.

2.2. Precompression Evaluation. Precompression factors of the blend were conducted before and after granulation as stated below.

2.2.1. The Angle of Repose. The funnel cone method was used to determine the angle of repose, by passing the precompression powder and granules of all the formulations, which is then calculated by measuring the height of the heap [18].

2.2.2. Bulk Density. A predetermined amount of powder was filled in a flask of 100 ml and volume noted for determining bulk volume [19], where

$$\rho_b = \frac{M}{\text{BulkVolume}}. \quad (1)$$

2.2.3. Tapped Density. Tapped density was calculated by tapping the cylinder 100 times and noting the change in volume by using the following formula [20]:

$$\rho_t = \frac{M}{\text{TappedVolume}}. \quad (2)$$

2.2.4. Carr's Index and Hausner's Ratio. The compressibility index can be used to predict the flow property and is based on density measurements [21]. Carr's index can be calculated as

$$\text{CI}(\%) = \frac{\rho_t - \rho_b}{\rho_t} \times 100. \quad (3)$$

Flowability of powder can be assessed by using the following formula:

$$\text{HR} = \frac{\rho_t}{\rho_b}. \quad (4)$$

2.3. Postcompression Evaluation

2.3.1. Weight Variation Test. Twenty tablets from each formulation were subjected to weight variation testing using a weighing balance (ATL 3000G/0.001G); all tablets must fulfill official requirements.

2.3.2. Thickness and Diameter. Thickness and diameter are one of the quality control parameters of tablet dosage form which need to be evaluated [21].

2.3.3. Hardness. Hardness test is one the quality control parameters used to determine the mechanical strength of the formulated tablet dosage form as appropriate hardness determines the quality of dosage form; the test is performed using a hardness tester (Galvano Scientific Model GHT-1) [21].

2.3.4. Friability. Friability test was conducted on an apparatus prescribed by USP. 10 tablets were dedusted, weighed, and placed in the apparatus which is revolved for 25 revolutions per minute for four minutes to calculate the change in weight tablets; the tablets were weighed again to determine the friability [18] using a friability tester (Galvano Scientific Model FT-L).

2.3.5. Disintegration Test. 6 tablets from each formulation were drawn randomly and were disintegrated in an apparatus recommended by USP using 900 ml of water to check the disintegration time for each tablet at 37 (±2°C) [21], using a disintegration apparatus (Galvano Scientific Model 121-L).

2.3.6. Assay of Tablets. Twenty tablets from each formulation were weighed to determine the average weight; the average weight quantity is drawn from the sample after crushing the tablets. The average quantity of powder was dissolved in water and methanol with a ratio of 50 : 10, which is then sonicated for 15 minutes; the volume was increased to 100 ml with water and filtered. Dilutions were made to identify the percent content of the drug by taking absorbance at 273 nm for caffeine and 243 nm for acetaminophen.

2.3.7. Dissolution Test. A dissolution test was conducted to determine the active release rate from the dosage form. In this test, 6 tablets are placed in each vessel of an apparatus suggested by USP for a specific period of time which is 12 hrs for extended release in physiological pH of the intestine at a maintained temperature of 37 ± 0.5°C at 75 rpm in a dissolution tester (model GDT-6L).

Known quantities of samples were drawn at different time intervals up to 12 hrs and were diluted to measure absorbance at a specified wavelength of acetaminophen and caffeine (243 nm and 273 nm, respectively) using a spectrophotometer [21].

2.3.8. Similarity Factor (f_2). The dissolution profile of formulated samples was compared with EF2; because of its best-fitted dissolution, it was considered as the standard product, while the other 2 were taken as test formulations [18]. The following equation was approved by FDA for the determination of the similarity factor between the test and the reference brand:

$$f_2 = 50 \times \log\left[\left\{1 + \left(\frac{1}{n}\right)\sum_{r-1}^{n} \mathrm{wt}(\mathrm{Ri} - \mathrm{Ti})^{0.5}\right\} \times 100\right]. \quad (5)$$

Ri and Ti are the drug release of the reference and test formulations in percentage after each interval of time, respectively, while N is the number of samples taken.

2.4. Model-Dependent Analysis of Dissolution Studies. The following are the kinetic models applied to the dissolution data: zero-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas [17].

When the drug release is independent of time, it is explained by the zero-order kinetic [22]:

$$Q_t = Q_o + K_o t. \quad (6)$$

The Higuchi model describes the relation between cumulative percentage drugs and square root of time [18]:

$$Q_t = Q_o e^{-Kt}, \quad (7)$$

whereas Hixson-Crowell's model shows the relationship between the cube root percentage drug remaining and time:

$$3\sqrt{Q_0} - 3\sqrt{Q_t} = K_{\mathrm{HC}} \cdot t. \quad (8)$$

Drug release from a polymeric system is explained by Korsmeyer et al. (1983) who suggested a simple relationship given as an equation:

$$F = \frac{M_t}{M_\infty} = K_m t^n. \quad (9)$$

The release kinetics of EF1-EF3 was studied through a model-dependent approach. The coefficient of correlation and rate constants of respective models were calculated.

3. Results

3.1. Precompression Quality Control Attributes. All the precompression parameters were up to the required quality control standards and are given in Table 2.

3.2. Postcompression Physical Quality Control Attributes. For EF1-EF3, the average weights in milligrams with standard deviation were 1288.05 (±5.698), 1300.7 (±5.63), and 1350.7(±3.278), respectively, and the hardness was found to be 7.19 (±0.09), 7.29 (±0.055), and 7.43 (±0.044). Thickness and diameter were, respectively, 8.85 (±0.006) and 19.41 (±0.01) for EF1, 8.88 (±0.004) and 19.41 (±0.004) for EF2, and 8.89 (±0.007) and 19.41 (±0.006) for EF3. Friability of all three formulations was *found to be less than 1%*. Drug content for all the formulations was found to be 97.25 (±0.330), 99.21 (±0.367), and 98.32 (±0.395), given in Table 3.

An assay of all formulations was conducted by taking absorbance at 259.5 nm which is an anisobestic wavelength for caffeine and acetaminophen. The assay was found to be 100.43 (±0.756) for EF1, 104.53 (±0.252) for EF2, and 98.32(±0.395) for EF3, given in Table 3.

3.2.1. Disintegration. Disintegration test indicated that the tablets were not disintegrated throughout the test; all were observed in their original form, only the size was reduced.

Table 2: Evaluation of precompression parameters of formulation EF1-EF3.

S. no	Formulation	Bulk density (gm/cm^3)	Tapped density (gm/cm3)	Hausner's ratio	Angle of repose (°)	Compressibility index (%)
Powder						
1	EF1	0.51	0.64	1.25	37°	25.49
2	EF2	0.55	0.64	1.16	38.1°	16.36
3	EF3	0.54	0.65	1.20	37°	20.37
Granules						
1	EF1	0.54	0.66	1.22	40°	22.22
2	EF2	0.55	0.63	1.15	36.4°	14.55
3	EF3	0.56	0.65	1.16	36.8°	16.07

Table 3: Evaluation of postcompression parameters of formulation EF1-EF3.

Formulation	Weight variation (mg (±SD)) ($n = 20$)	Hardness (KG (±SD)) ($n = 20$)	Thickness (mm (±SD)) ($n = 20$)	Diameter (mm (±SD)) ($n = 20$)	Friability (%) ($n = 10$)	Assay (%) ($n = 3$)
EF1	1288.05 (±5.698)	7.19 (±0.09)	8.85 (±0.006)	19.41 (±0.01)	0.46	100.43 (±0.756)
EF2	1300.7 (±5.63)	7.29 (±0.055)	8.88 (±0.004)	19.41 (±0.004)	0.46	104.53 (±0.252)
EF3	1350.7 (±3.278)	7.43 (±0.044)	8.89 (±0.007)	19.41 (±0.006)	0.96	98.32 (±0.395)

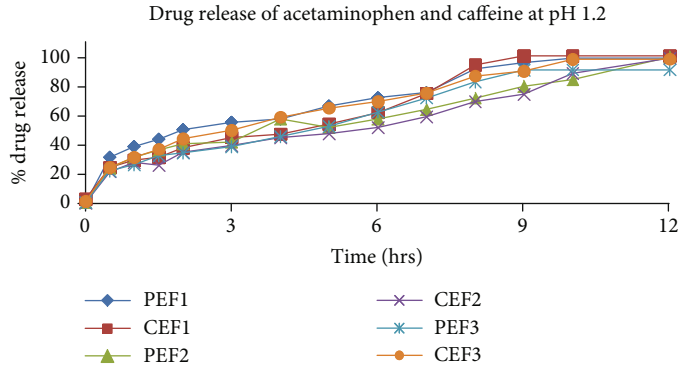

Figure 1: Drug release profile of acetaminophen and caffeine at pH 1.2.

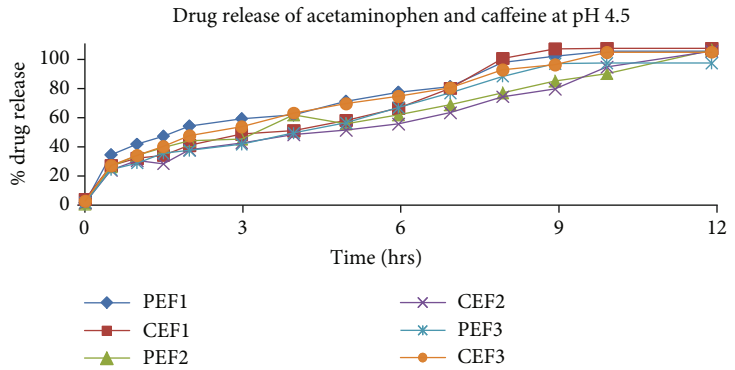

Figure 2: Drug release profile of acetaminophen and caffeine at pH 4.5.

3.2.2. Dissolution. For 12 hrs of dissolution, caffeine was released from EF1 with the percentage release in the range from 99.85% to 100.65%, EF2 had a release ranging from 99.32% to 100.28%, and EF3 had a release from 98.09% to 100.77%. For acetaminophen, the percent release of EF1 was from 99.81% to 100.91%, from 100.24% to 100.91% for EF2, and from 86.81% to 95.73% for EF3 for 12 hours as shown in Figures 1–3.

EF2 is considered as the most optimized drug among the three formulations containing Eudragit (EF1-EF3). The release rate of acetaminophen from the matrix system also suggested that EF2 is a superior formulation among all, as

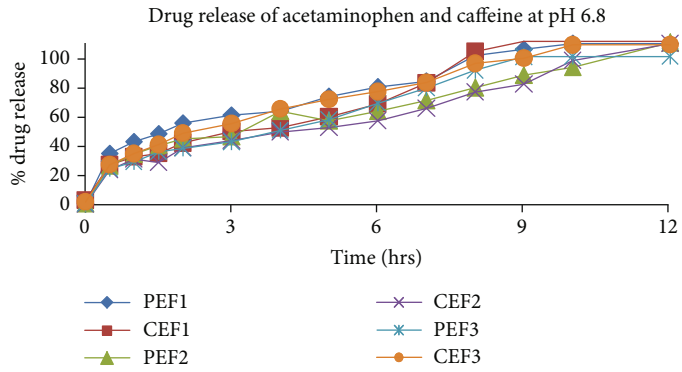

Figure 3: Drug release profile of acetaminophen and caffeine at pH 6.8.

the maximum amount of acetaminophen was released at 9 hrs, 9 hrs, and 8 hrs from EF1 at pH 1.2, 4.5, and 6.8, while EF3 had a maximum release of up to 10 hrs, 10 hrs, and 9 hrs at pH 1.2, 4.5 and 6.8, respectively. EF2 has a controlled release rate with maximum release at 12 hrs of dissolution in all tested dissolution media. EF1 released the maximum amount of caffeine from a matrix containing hydrophobic polymer at 9 hrs at pH 1.2 while EF3 released the maximum amount at the 10th hr of dissolution, so EF2 is considered as the better formulation among all. At pH 4.5, more than 90% of caffeine was released after 7 hrs of dissolution from EF1 and EF3 while EF2 retarded the release up to 12 hrs. At pH 6.8, EF1 and EF3 released 90% of the drug after 8 hrs like at pH 4.5, but EF2 showed a consistent increase in release concentration over the period of 12 hrs indicating EF2 as the optimized product among all.

3.3. Kinetic Model-Dependent Analysis of Dissolution. There are several kinetic model-dependent methods used to study the release kinetics of drugs like zero-order, first-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas that are used to determine the release kinetics of drugs from the dosage form [4, 23].

On applying the release data of caffeine and acetaminophen from matrix tablets on DDSolver, the best-fitted model among the zero-order, Higuchi, Hixson-Crowell, and Korsmeyer-Peppas models had a best-fitted r^2 value of caffeine that lies between 0.938 and 0.992 at pH 1.2, while0.960 and 0.994 and 0.989 and 0.947 at pH 4.5 and 6.8, respectively. Values of r^2 ranges in between 0.994-0.985, 0.993-0.981, and 0.963-0.985 when applied on the dissolution data of release of acetaminophen at pH 1.2, 4.5, and 6.8 are given in Table 4.

3.3.1. Similarity Factor (f_2). Release of acetaminophen from EF3 resembled EF2 at pH 1.2, 4.5, and 6.8, while the EF1 release was similar at pH 4.5 and 6.8, while the release was dissimilar for caffeine from both formulations in all three pH solutions given in Table 5.

The similarity factor (f_2) was applied on dissolution profiles of caffeine and acetaminophen in different pH conditions; EF2 was taken as the reference because of its maximum release retardation while the other formulations were the tested formulations. It is concluded that formulation EF1 acetaminophen release was similar to EF2 while caffeine release was dissimilar in all pH conditions. EF3 acetaminophen release was similar at pH 4.5 and 6.8, while at pH 1.2, release was dissimilar, i.e., 48.76 while caffeine release was dissimilar in all pH conditions.

4. Discussion

Eudragit RS 30D is available as a latex-like liquid dispersion, and it is a methacrylic ester polymer [8, 9]. The possible mechanism of release of drug in such a type of tablet is diffusion [9, 10]. Solute transport from nondegradable polymeric systems is mainly considered as diffusion driven (Fu and Kao 2010; Thakral, Thakral et al. 2013). A hydrophobic system is not suitable for poorly soluble drugs because their release rate is slow due to low concentration gradient (Dash and Verma 2013).

EF2 is considered as the most optimized drug among the three formulations containing Eudragit (EF1-EF3). Release rate of acetaminophen from the matrix system also suggested that EF2 is a superior formulation among all, as the maximum amount of acetaminophen was released at 9 hrs, 9 hrs, and 8 hrs from EF1 at pH 1.2, 4.5, and 6.8, while EF3 has a maximum released drug up to 10 hrs, 10 hrs, and 9 hrs at pH 1.2, 4.5 and 6.8, respectively. EF2 has a controlled release rate with maximum release at the 12th hr of dissolution in all tested dissolution media. EF1 released the maximum amount of caffeine from the matrix containing hydrophobic polymer at 9 hrs at pH 1.2 while EF3 released the maximum amount at the 10th hr of dissolution, so EF2 is considered as the better formulation among all. At pH 4.5, more than 90% of caffeine was released after 7 hrs of dissolution from EF1 and EF3 while EF2 retarded the release up to 12 hrs. At pH 6.8, EF1 and EF3 released 90% of the drug after 8 hrs like at pH 4.5, but EF2 showed a consistent increase in release concentration over the period of 12 hrs indicating EF2 as the optimized product among all.

Controlled release formulations are prepared with an intention to control the release of the drug over a period of time with the maintenance of effective drug concentration within the blood or plasma, for which different mathematical models are applied for the prediction of release kinetics of the controlled release dosage form [3, 4].

There are several kinetic model-dependent methods used to study the release kinetics of drugs like zero-order, first-order, Hixson-Crowell, Higuchi, and Korsmeyer-Peppas that are used to determine the release kinetics of drugs from the dosage form [4, 22].

Table 4: Release kinetics of acetaminophen and caffeine from formulation EF1-EF3.

		Acetaminophen			Caffeine		
pH 1.2		EF1	EF2	EF3	EF1	EF2	EF3
Zero-order	K^0	10.686	9.742	9.546	10.396	8.877	10.350
	r^2	0.536	0.804	0.815	0.830	0.820	0.693
Hixson-Crowell	K^{HC}	0.072	0.055	0.052	0.060	0.045	0.065
	r^2	0.859	0.949	0.938	0.917	0.878	0.929
Higuchi	K^H	30.765	27.581	26.936	29.234	24.966	29.561
	r^2	0.962	0.990	0.963	0.943	0.939	0.991
Korsmeyer-Peppas	k^{KP}	35.852	25.174	23.403	24.145	21.307	30.552
	r^2	0.9766	0.9934	0.9699	0.955	0.948	0.992
pH 4.5		EF1	EF2	EF3	EF1	EF2	EF3
Zero-order	K^0	9.514	9.728	0.1579	12.037	9.252	11.327
	r^2	0.858	0.808	0.125	0.1579	0.7402	0.5045
Hixson-Crowell	K^{HC}	0.050	0.055	0.8663	0.125	0.050	0.092
	r^2	0.911	0.949	35.609	0.8663	0.8943	0.9497
Higuchi	K^H	26.672	27.530	0.802	35.609	26.298	32.770
	r^2	0.943	0.989	52.566	0.802	0.982	0.966
Korsmeyer-Peppas	k^{KP}	21.179	24.965	0.973	52.566	25.955	38.312
	r^2	0.960	0.993	12.037	0.973	0.982	0.982
pH 6.8		**EF1**	**EF2**	**EF3**	**EF1**	**EF2**	**EF3**
Zero-order	K^0	9.028	9.010	8.789	11.489	9.688	11.739
	r^2	0.981	0.988	0.979	0.726	0.748	0.650
Hixson-Crowell	K^{HC}	0.046	0.045	0.045	0.084	0.055	0.093
	r^2	0.916	0.942	0.951	0.992	0.921	0.997
Higuchi	K^H	25.275	25.068	24.752	32.739	27.555	33.677
	r^2	0.943	0.937	0.975	0.941	0.989	0.947
Korsmeyer-Peppas	k^{KP}	19.586	17.158	20.829	30.548	26.961	34.276
	r^2	0.9626	0.9744	0.9853	0.943	0.989	0.947

Table 5: f_2 similarity.

Formulations	Acetaminophen			Caffeine		
	pH 1.2	pH 4.5	pH 6.8	pH 1.2	pH 4.5	pH 6.8
EF1	61.62 (S)	52.08 (S)	66.06 (S)	46.24 (DS)	39.21 (DS)	38.83 (DS)
EF3	46.82 (DS)	61.95 (S)	52.18 (S)	32.35 (DS)	36.52 (DS)	33.81 (DS)

The similarity factor (f_2) was applied on dissolution profiles of caffeine and acetaminophen in different pH conditions; EF2 was taken as the reference because of its maximum release retardation while the other formulations were the test formulations. It is concluded that formulation EF1 acetaminophen release was similar to EF2 while caffeine release was dissimilar in all pH conditions. EF3 acetaminophen release was similar at pH 4.5 and 6.8, while at pH 1.2, the release was dissimilar, i.e., 48.76 while caffeine release was dissimilar in all pH conditions.

5. Conclusion

EF2 contained Eudragit RS 30D that was a hydrophobic polymer latex that has retarded the release of active pharmaceutical from a matrix tablet dosage form; other excipients used to form a stable dosage form were magnesium stearate, talcum, and lactose that were used as lubricant, disintegrating agent, and wetting agent.

Eudragit RS 30D containing formulation EF2 can be used in the future in order to treat several pain conditions

especially since it can be prescribed for pain associated with arthritis as it will cause analgesia for a 12-hour duration, thus causing decrease in dosing frequency.

Data Availability

No data have been adapted from any research or paper; all the data have been collected in the research lab while the standards were taken from the official guideline (USP).

Conflicts of Interest

All contributing authors are academicians and researchers. The first author, Ms. Lailoona Jawed, is an assistant professor in the Department of Pharmaceutics, Faculty of Pharmacy, Jinnah University for Women, Karachi. The second author, Dr. Huma Dilshad, is a research co-supervisor, and the third one, Dr. Ghulam Sarwar, is a research supervisor and dean, Faculty of Pharmacy, Jinnah University for Women, and also provided research guidance; all are full-time teaching faculty members in the Department of Pharmaceutics, Faculty of Pharmacy and Pharmaceutical Sciences, Jinnah University for Women.

Authors' Contributions

All authors participated fully throughout the study period. The concept of the study was proposed by Dr. Huma Dilshad. Ms. Lailoona Jawed conducted the whole study and contributed in data collection and literature survey under the supervision of Dr. Huma Dilshad. Prof. Dr. Ghulam Sarwar, the research project supervisor, provided guidance in data analysis and interpretation.

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