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Development of Release Control Formulations of Dexlansoprazole and Pharmacokinetic Evaluation

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덱스란소프라졸의 방출 조절 제제 개발 및 약물동태학적 평가

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Abstract This study focused on enhancing dosage convenience and simplifying the manufacturing process by dosage form change from traditional pellets to tablets of Dexlansoprazole. The prepared formulations were systematically evaluated for efficacy through a compatibility test that selected stable excipients for use with amorphous dexlansoprazole. Formulations with varying release patterns were evaluated by changing excipient ratios. The delayed-release formulation, incorporating a sustained release agent, exhibited an inability to mimic the absorption profile observed in the control drug pellet formulations. In contrast, an immediate release formulation's dissolution pattern manifested absorption levels comparable to those of the control drug. The pharmacokinetic evaluation in beagle dogs to assess equivalence to the conventional double delayed release pellet formulation showed that the AUCt of the immediate release formulation had a confidence interval of 0.7318 to 1.1511 and the Cmax had a confidence interval of 0.8117 to 1.4609, indicating that the lag time could be increased by increasing the enteric coating percentage, which could further delay the Tmax and slow the dissipation rate, resulting in a formulation equivalent to the control. In summary, this study demonstrates the feasibility of producing a stable amorphous product while simplifying manufacturing.

요 약 덱스란소프라졸은 오리지널 의약품의 특허 회피 어려움과 제형 변경의 한계로 업계에서 제네릭 개발이 늦어지는 대표적인 약물로서 본 연구에서는 특허를 회피하고 제형적 한계를 극복하기 위하여 복용 편의성과 공정 단순화를 통해 종래의 펠렛에서 정제로 제형을 변경, 제조하고 그 결과를 평가하였다. 무정형 덱스란소프라졸과 첨가제 간의 적절한 배합성 검토 시험을 통해 안정적인 첨가제가 선택되었으며, 두 가지 다른 방출 패턴으로 첨가제의 비율을 변화시켜 제조한 결과, 서방화제를 활용한 지연방출제제는 표면적이 넓은 펠렛 제형 대조약의 흡수를 재현하지 못하지만, 즉시 방출제제의 용출 패턴을 통해 대조약과 동등한 수준의 흡수 패턴을 나타낼 수 있음이 확인되었다. 또한, 비글견에서의 약물동태학적 평가를 통해 종래의 이중 지연방출 펠렛 제형과의 동등성을 평가한 결과, 즉시방출제제에서의 AUCt의 신뢰값은 0.7318 ~ 1.1511, Cmax의 신뢰값은 0.8117 ~ 1.4609로 장용코팅의 비율을 늘려 Lag time을 늘리면 Tmax를 좀 더 늦출 수 있고, 이에 따른 소실 속도를 늦추어 대조약과 동등한 수준의 제제가 가능하다는 것을 알 수 있었다. 본 결과를 통해 제품 안정성을 확보하고 제조 방법을 단순화한 무정형의 제품을 생산 할 수 있을 것으로 사료된다.

Keywords : Dexlansoprazole, Immediate-Release, Sustained-Release, Tablet Formulation, Beagle Dog

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1. Introduction

The chemical name of Dexlansoprazole is (+)-2-[(R)-{[3-methyl-]4-(2,2,2-trifluoroethoxy)pyridin-2-yl]methyl}sulfinyl]-1H-benzimidazole and has the (R)-(+) enantiomer of lansoprazole, a racemic mixture of (R)-(+) and (S)-(-)(Fig. 1). The two enantiomers are stereo-selectively metabolised in the human body and have different pharmacokinetic profiles, with (+)-lansoprazole being more effective than (-)-lansoprazole due to its higher bioavailability and lower side effects[1]. Dexlansoprazole is a newer member of the proton pump inhibitor (PPI) class, and pharmaceutical products containing this prodrug are indicated for the treatment of erosive esophagitis, maintenance treatment of erosive esophagitis, and heartburn associated with symptomatic non-erosive gastroesophageal reflux disease[2]. For the treatment of erosive esophagitis, dexlansoprazole 60 mg orally once daily for up to 8 weeks and for maintenance after treatment of erosive esophagitis, dexlansoprazole 30 mg orally once daily for up to 6 months in adults. In adolescents aged 12 years and older, dexlansoprazole 30 mg orally once daily for up to 16 weeks. For the treatment of Gastroesophageal reflux disease symptoms, dexlansoprazole 30 mg orally once daily for 4 weeks[3-5]. The H+/K+ ATPase in the gastric wall cells involved in acid secretion hydrolyses ATP and exchanges H+ from the cytoplasm for K+ in the secretory canaliculus, allowing hydrochloric acid to be secreted into the gastric cavity. Dexlansoprazole inhibits the H+/K+ ATPase and thus inhibits the secretion of hydrochloric acid. Orally administered dexlansoprazole is absorbed in the duodenum and small intestine, passes through the liver and reaches the gastric wall cells, where it is converted to sulphenamide and inhibits proton pump activity in an acidic environment[6,7].

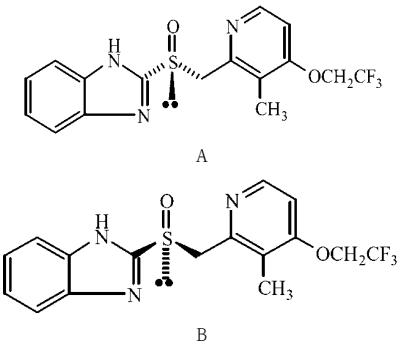

Fig. 1. Chemical structure of A : (R)-(+)-lansoprazole, B : (S)-(-)-lansoprazole

The currently marketed control drug, Dexilant DR Capsule®(Takeda Pharmaceuticals, Japan), is a dual delayed release formulation of pellets with two release patterns in a 25:75 ratio filled into hard capsules, and two plasma concentration peaks are detected at 1-2 hours and 4-5 hours after administration, resulting in prolonged efficacy[8,9]. However, the above formulation has the following problems. Firstly, the production yield is low because the pellets have to be prepared using a fluidised bed granulator, and the unit manufacturing cost is high due to the complex production process of preparing two types of pellets and filling them into one capsule. Second, the formulation is entirely imported from Japan. Thirdly, the composition patent and crystallisation patent of the drug prevent the development of generics and limit market access[10]. Therefore, this study aimed to solve the existing problems by designing a formulation containing dexlansoprazole, circumventing the patent of the marketed formulation and modifying the formulation into enteric-coated tablets. To verify the efficacy of the modified formulation, Comparative dissolution studies and pharmacokinetic investigations in beagle dogs were conducted to evaluate the developmental prospects.

2. Material and Methods

2.1 The materials and instruments for experiment

Dexlansoprazole was purchased from Amino Chemicals Ltd.(Malta). Magnesium carbonate (MgCO3) was purchased from Tomita(Japan), potassium hydroxide(KOH) from Merck(Germany), D-mannitol(Pearlitol® 200SD) from Roquette (France) and magnesium metasilicate(Neusilin® US2) from Fuji Chemical(Japan), Low-substituted hydroxypropylcellulose(L-HPC, LH11) from Shin-Etsu(Japan), poly vinyl pyrrolidone(PVP), crosspovidone(Kollidon®CL) from BASF(Germany) and sodium croscarmellose(Primellose®) from DEF Pharma(Germany), Microcrystalline cellulose (Ceolus™) from Asahi Kasei(Japan), pregelatinised starch (Starch1500®) from Colorcon(USA), L-arginine from Target(Korea), calcium hydrogen phosphate anhydrous(A-Tab®) from Innophos(USA), silicon dioxide(Aerosil®200) from Evonik(Germany), sodium stearyl fumarate(PRUV®) from JRS(Germany), Opadry white 03B28796 from Colorcon(China), hypromellose phthalate(HPMCP®) from Shin-Etsu (Japan), polyethylene glycol 6000(Macrogol®6000SP) from Sanyo(Japan) and titanium oxide(TiO2) from Kirsch(Germany). Takeda Pharmaceuticals' DEXILANT® DR Capsule 60 mg was used as the control drug, which was notified by the Ministry of Food and Drug Safety. The tablet machine was KT-18SS(KeumSumg Machinery, Korea), the Kneader was KMLC(KeumSumg Machinery, Korea), the granulator was TSP-∅130(Seoul HiTech, Korea), the fluidized bed dryer was JIT-FBG10(J-ITec, Korea), the mixer was DM-0.6(J-ITec, Korea) and the coater was KC50FC(KumSung Machinery, Korea).

2.2 Formulation compatibility and quantification test

Dexlansoprazole and each excipient were combined in a 1:1 (w/w) ratio within a 20 mL clear glass vial, followed by thorough mixing. The resulting samples were stored in a stability chamber under accelerated conditions(40℃/75% RH) for a duration of four weeks. Periodically, samples were withdrawn throughout the storage period and subjected to quantitative analysis to assess the mixture compositional integrity. During the storage period, samples were taken periodically and tested for content to evaluate formulation compatibility. In addition, by including MgCO3, a stabiliser, in the raw material of dexlansoprazole, samples are prepared in equal proportions of each additive at 1:1:1 (w/w) and stored in a stability chamber under accelerated test conditions (40℃/75%RH) for 4 weeks. The samples were visually observed for discolouration and caking, and content tests were performed to evaluate changes over time. Add 20 mL of diluent to the sample prepared in the above 20 mL glass vial to dissolve it sufficiently, then take 5 mL and place it in a 100 mL volumetric flask, and the liquid labelled as diluent is the test liquid. Separately, 25 mg of dexlansoprazole standard was accurately weighed and placed in a 100 mL volumetric flask, and the liquid marked with the diluent was used as the standard (diluent: 55:45 (w/w) of methanol and 0.1 M sodium hydroxide). The analysis was performed by HPLC under the following conditions. The HPLC system was an LC-4000 HPLC(Jasco, Japan), and the detector was an ultraviolet visible spectro -photometer at 258 nm. The column was a Capcellpak C18(5 μm, 4.6 mm × 250 mm) column and the column temperature was 35°C. The mobile phase was a 55:45 (w/w) solution of 0.02 N ammonium acetate and acetonitrile, the flow rate was 1.0 ml/min.

2.3 Tablet Preparation and Evaluation

To prepare sustained release tablet, dexlansoprazole, D-mannitol, Neusilin® US2, L-HPC and polyvinylpyrrolidone were combined with a binder containing potassium hydroxide by wet granulation. After drying and granulation,

the granules were mixed with crosspovidone, microcrystalline cellulose, silicon dioxide and sodium stearyl fumarate. For immediate release tablet preparation, dexlansooprazole, MgCO3, D-mannitol, microcrystalline cellulose, L-arginine, crosspovidone, croscarmellose sodium, anhydrous calcium hydrogen phosphate and sodium stearyl fumarate were mixed by direct tabletting. The mixture was stirred and sprayed with a coating solution prepared from Opadry White® for an initial coating. For the enteric coating, a coating solution of HPMCP, PEG6000 and TiO_2 is sprayed for the second coating. The proportions of additives for each method are given in Table 1. The formulations have been carefully researched in the literature to select the most ideal one. Tablet hardness was measured with a hardness tester and friability with an friability tester. Disintegration was measured using a disintegration tester according to the test method of the Korean Pharmacopoeia.

2.4 Dexlansoprazole Comparative Dissolution and Quantification Test

The comparative dissolution test method was based on the method published in the FDA Dissolution Method, using the second method (paddle method) as the test method, the rotation speed was 75 rpm, the dissolution test solution was 900 mL of sodium lauryl sulfate at a concentration of 0.144% in pH 7.0 phosphate buffer, and the sample collection time was 10, 20, 30, 40, 50, 60, 75, 105, 120, 180, 240 minutes. Controls were performed using a sinker. The dissolution medium collected above was used as a test liquid, and 66.7 mg of dexlansoprazole standard was accurately weighed into a 100 mL volumetric flask and marked with a diluent to serve as the standard. Take 5 mL of the standard solution and place it in a 50 mL volumetric flask and use it as a standard. Measurement was performed by UV visible spectrophotometer with 258 nm wavelength.

2.5 Pharmacokinetic Studies in Beagle Dogs

A comprehensive pharmacokinetic investigation was undertaken, involving of 15 male beagle dogs with an age range of 27 to 29 months. Two formulations of the test drug and a control drug were administered orally and study design was a three arm, two period crossover study design. Blood samples were systematically collected at 15 specific time points over a 24 hour period, Subsequently, the collected plasma underwent meticulous pretreatment and analysis utilizing LC-MS/MS methodology to precisely determine the concentration of dexlansoprazole in the plasma. The resulting drug concentration time curve data were subjected to rigorous statistical processing to glean valuable insights into the pharmacokinetic profile of the test drug.

3. Results and Discussion

3.1 Formulation Compatibility and Quantification Test

The formulation compatibility and quantification test provided that the additive did not interfere with the peak of dexlansoprazole, thereby ensuring a high degree of specificity in the analytical method. Additionally, the linearity of the assay was established with a correlation coefficient (R^2) of 0.9995, substantiating the method's ability to maintain a linear relationship between analyte concentration and response(Fig. 2). In the analysis of samples featuring a 1:1 (w/w) ratio of dexlansoprazole to additives, notable observations were made. Specifically, discolouration and caking manifested in all additives, except for KOH and MgCO3, which acted as stabilisers. The observed undesirable effects exhibited a discernible decline by week 4, suggesting a dynamic evolution of the stability profile over time. These findings contribute valuable insights into the formulation dynamics and stability of the investigated drug.

Table 1. Formulation compositions of Dexlansoprazole tablet

Ingredients	Amount per tablet(%)							
	DST-01	DST-02	DST-03	DST-04	DST-05	DST-06	DST-07	DST-08
Dexlansoprazole	12.8	12.8	12.8	12.8	12.8	12.8	12.8	12.8
Potassium Hydroxide	3.2	3.2	3.2	3.2	-	-	-	-
Magnesium Carbonate	-	-	-	-	2.8	2.8	2.8	2.8
D-Mannitol	32.1	32.1	32.1	32.1	18.2	18.2	18.2	18.2
Magnesium Aluminometasilicate	7.7	7.7	7.7	7.7	-	-	-	-
Low-Substituted Hydroxypropyl Cellulose	9.4	9.4	9.4	9.4	-	-	-	-
L-Arginin	-	-	-	-	13.9	13.9	13.9	13.9
polyvinylpyrrolidone K30	6.4	-	-	-	-	-	-	-
polyvinylpyrrolidone K90	-	4.3	6.4	8.6	-	-	-	-
Crospovidone	1.1	1.1	1.1	1.1	-	3.2	6.4	12.8
Croscarmellose Sodium	-	-	-	-	-	1.1	3.2	5.4
Microcrystalline Cellulose	11.1	13.3	11.1	9.0	24.6	20.3	15.0	6.4
Dicalcium Phosphate, Anhydrous	-	-	-	-	10.7	10.7	10.7	10.7
Silicon Dioxide	1.7	1.7	1.7	1.7	2.6	2.6	2.6	2.6
Sodium Stearyl Fumarate	2.1	2.1	2.1	2.1	2.1	2.1	2.1	2.1
Opadry white 03B28796	3.4	3.4	3.4	3.4	3.4	3.4	3.4	3.4
Hypromellose Phthalate	5.5	5.5	5.5	5.5	5.5	5.5	5.5	5.5
Polyethylen Glycol6000	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Titaum Dioxide	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8

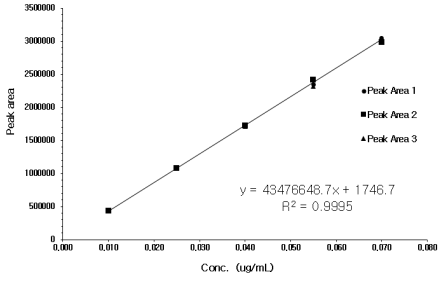

Fig. 2. Linearity of Compatibility assay

Since it is unclear to judge the results of the formulation compatibility test without the addition of a stabiliser, we tested dexlansoprazole with a 1:1:1 (w/w) ratio of additives, including MgCO3 as a stabiliser, and no discolouration was observed, caking was observed only in some raw materials, and the content results all met the standards of 95~105 %(Table 2).

3.2 Tablet Preparation and Evaluation

The amorphous form of dexlansoprazole utilized in this investigation is distinguished by its small particle size and elevated static electricity, meticulous attention was directed towards the optimization of the wet granulation process. The advantage was to ameliorate the flowability characteristics of the drug particles and mitigate the undesirable generation of static electricity. This strategic refinement aimed not only to enhance the overall handling and processing capabilities of the drug during tablet preparation but also to ensure the reproducibility and efficiency of the subsequent manufacturing processes involved in the formulation of pharmaceutical tablets containing dexlansoprazole[11]. The wet granulation process also has advantage in controlling the sustained release of retardants[12]. Disadvantages included the difficulty in ensuring the stability of dexlansoprazole due to exposure to moisture and the possibility of temperature dependent discolouration during the drying process. The coalescence time of 5 minutes or more was required.

Table 2. Compatibility Test result of Dexlansoprazole in accelerated(40℃/75% RH) for 4 weeks

Function	Excipients	1:1(w/w)Assay (%)			1:1:1(w/w)Assay (%)		
		initial	2 weeks	4 weeks	initial	2 weeks	4 weeks
API	Dexlansoprazole	99.2	92.3	50.4	-	-	-
Stabilizers	KOH	98.6	100.1	100.5	-	-	-
	$MgCO_3$	98.3	99.4	98.7	-	-	-
Diluent	D-Mannitol	99.6	90.5	10.3	100.2	99.6	98.7
	Lactose Hydrate	97.6	86.3	9.2	99.8	98.9	98.2
	Microcrystalline Cellulose	99.4	83.9	22.5	99.4	98.7	98.5
	Neusilin®	98.2	81.7	20.3	100.1	97.6	96.3
	Starch1500®	99.7	84.5	32.2	100.0	98.4	98.5
	A-Tab	99.5	86.3	31.8	99.6	99.2	98.7
	L-Arginin	98.6	98.5	97.8	100.0	98.6	98.1
Sustained release excipients	Hypromellose2910	89.4	82.7	15.2	97.6	97.2	96.4
	polyvinylpyrrolidone K30	98.1	88.3	20.7	99.3	97.6	97.8
	polyvinylpyrrolidone K90	98.7	87.6	16.4	98.9	96.7	96.5
Disintegrant	Low-Substituted Hydroxypropyl Cellulose	100.8	83.7	16.6	98.7	97.8	97.7
	Primellose®	100.1	88.4	23.0	99.5	98.2	97.3
	Crospovidone	99.7	91.5	20.4	97.7	98.4	96.4
Lubricant	SiO_2	98.7	87.9	11.7	98.2	98.7	96.5
	PRUV®	99.2	100.4	20.6	100.1	99.1	99.3

The degree of discolouration after drying the copolymer at 50°C, 60°C and 70°C was determined, and drying at 50°C or lower was suitable. To ensure the stability of dexlansoprazole, the direct dosage method was optimized to avoid exposure to moisture and to favor the immediate release formulation. The direct tablet method is advantageous in terms of stability due to the simplicity of the manufacturing process, low batch to batch variation and low physical stress on the drug [13]. Disadvantages include poor flowability of the mixture, which can cause individual variations in the tabletting process, and the use of a screw hopper to assist powder flow from the hopper to the feeder[14]. During the mixing process, mixing times of 10, 15 and 20 min were used to test the uniformity of the mixture and 15 min was found to be sufficient. Tablet hardness, friability and disintegration time were measured to assess the physical specifications and quality control of the delayed-release and immediate release formulations containing dexlansoprazole. The friability criteria of each formulation met the standard of 0.5 % or less, and the hardness varied between the delayed release and immediate release formulations. According to the disintegration test, acid resistance was confirmed in the first solution from DST-01 to 07, but in DST-08, two out of six tablets failed acid resistance in the first solution(pH 1.2). In the second solution(pH 6.8), the disintegration time was delayed due to the effect of the preservative added in the delayed release formulation. The disintegration time was delayed depending on the type and amount of preservative. In the immediate release formulation, the disintegration time was controlled by the amount of preservative added(Table 3).

Table 3. Post compression characteristic of tablet

No.	Hardness (kp, n=5)	Friability (%, n=16)	Disintegration Time(min, n=6)
DST-01	9.21±0.83	0.01	26±1.37
DST-02	9.37±0.76	0.01	42±1.63
DST-03	9.15±0.48	0.01	58±2.32
DST-04	9.23±0.64	0.01	72±2.25
DST-05	12.62±1.21	0.00	18±1.72
DST-06	13.25±1.43	0.00	15±1.17
DST-07	13.54±1.37	0.00	9±1.03
DST-08	13.18±1.64	0.00	2±0.52(2T OOS)

3.3 Dexlansoprazole Comparative Dissolution and Quantification Test

The validation results confirmed that the additives did not affect the absorbance of dexlansoprazole, thus ensuring specificity, and the correlation coefficient (R^2) of linearity was greater than 0.995, thus ensuring linearity. The control drug is a capsule formulation filled with two types of pellets with different release patterns, 25% of the drug is released in the first phase and the remaining 75% of the drug is released in the second phase, and a step-like pattern is clearly visible in the comparative release graph[15]. Since the purpose of this study is to evaluate different release patterns for formulation modification, a comparative release test was conducted by adjusting the amount of PVP K90, a sustained release agent, through a wet granulation process to implement a delayed release pattern. In addition, a comparative dissolution test was carried out to check the immediate release pattern by adjusting the amount of disintegrant by direct dosage method. As it is not possible to achieve the dual release pattern of the control drug with a single matrix, release was controlled by adjusting the PVP so that the matrix could withstand 75% of the control drug release without complete disintegration. The release patterns of the formulations were systematically evaluated, with distinct characteristics observed for each. The DST-01 formulation, incorporating PVP K30 at a rate of 6.2%, exhibited a rapid release pattern, wherein all tablets disintegrated within a remarkably short duration of 30 minutes. In contrast, the DST-02, DST-03, and DST-04 formulations employed PVP K90 with higher viscosity, each at rates of 4.1%, 6.2%, and 8.3%, respectively, resulting in progressively delayed release patterns. After a comprehensive analysis of the release profiles, the DST-04 formulation emerged as the optimal choice due to its ability to achieve drug release within the predefined control range of 90 to 105 minutes(Fig. 3).

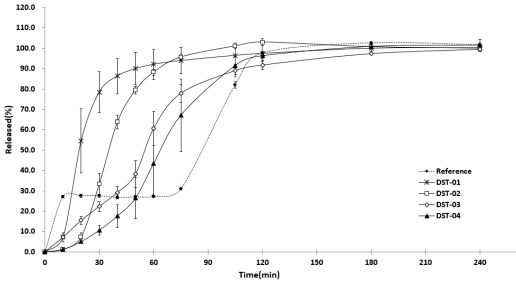

Fig. 3. Dissolution profiles of sustained release formulation in pH7.0 phosphate buffer and 0.144 % Sodium Lauryl Sulfate

A deliberate strategy was devised to design an immediate release pattern for the investigational formulation that would markedly surpass the release pattern of the control drug. This meticulous planning aimed to capitalize on the inherent characteristics of the high surface area pellet in the control drug formulation, strategically aligning the immediate release pattern to achieve an accelerated and efficacious drug release profile. This approach not only underscores the intricacies of formulation design but also demonstrates a thoughtful consideration of the specific attributes of the control drug, with the ultimate goal of optimizing therapeutic outcomes and enhancing patient compliance. The DST-05 formulation disintegration did not occur until 240 minutes. In DST-06, 07 and 08 formulations, disintegrant was added at 4.1 %, 9.3 % and 17.6 % and the disintegration rate of DST-06 and DST-07 increased with increasing percentage of disintegrant, but DST-08 disintegrated without ensuring acid resistance under acidic conditions due to excessive disintegrant and showed low disintegration rate under buffer conditions. Therefore, the DST-07 formulation was finally selected because it showed an immediate release pattern while maintaining acid resistance(Fig. 4).

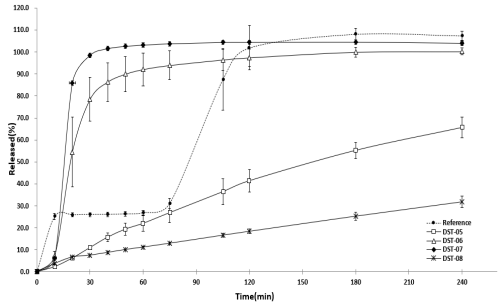

Fig. 4. Dissolution profiles of immediate release formulation in pH7.0 phosphate buffer and 0.144 % Sodium Lauryl Sulfate

3.4 Pharmacokinetic Studies in Beagle Dogs

Pharmacokinetic studies were conducted in beagle dogs using the reference drug and the delayed release formulation DST-04 as test drug 1 and the immediate release formulation DST-07 as test drug 2[16,17]. After oral administration, the time to peak plasma concentration of dexlansoprazole was 2.33 hour for the reference drug, 2.90 hour for test drug 1, and 1.30 hour for test drug 2. The area under the plasma concentration-time curve (AUCt) was 10661.97 ng·hr/ml, 4924.18 ng·hr/ml, 9106.58 ng·hr/ml, and the maximum plasma concentration (Cmax) was 3853.20 ng/ml, 1754.50 ng/ml, 3978.76 ng/ml, respectively. Test drug 1, a delayed release formulation, showed a delayed Tmax compared to the reference drug, while test drug 2, an immediate release formulation, showed a faster Tmax. However, the Cmax for test drug 1 was approximately half that of the reference drug and was similar for test drug 2. This suggests that the delayed-release formulation prevented complete absorption in the gastrointestinal tract due to the formulation difference, whereas the immediate-release formulation allowed maximum absorption through rapid dissolution. The 90% confidence interval for the log transformed mean difference in AUCt was log 0.2814 – log 0.5515 for test drug 1 and log 0.7318 – log 1.1511 for test drug 2. For Cmax, the interval was log 0.2076 – log 0.5309 for test drug 1 and log 0.8117 - log 1.4609 for test drug 2. Test drug 1 had significantly lower AUCt and Cmax, indicating incomplete absorption. Test drug 2 slightly exceeded the reference limits for AUCt and Cmax, but with a T/R ratio of 0.9178 for AUCt and 1.0890 for Cmax, the results were considered highly significant considering the group size (Fig. 5).

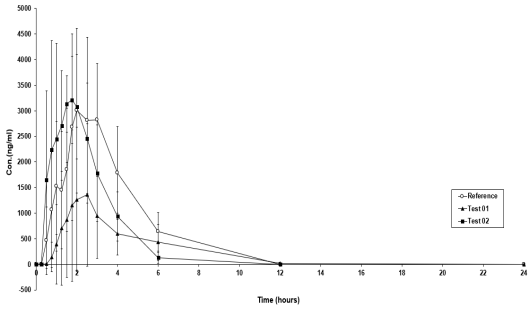

Fig. 5. Mean concentration-time profile of Dexlansoprazole in beagle dog plasma Dexilant DR Cap. 60mg (Reference)(◊), DST-04(Test 01) (▲), DST-07 (Test 02) (■) (mean±S.D., n=15)

4. Conclusion

Dexlansoprazole is a novel proton pump inhibitor for which the industry has experienced delays in generic development due to challenges in circumventing the patent protection of the originator product and overcoming formulation limitations. Particular concern is the expected increase in prescription volumes, raising concerns about potential royalty outflows to foreign companies due to reliance on imported medicines. The unique concept of dual extended release poses significant challenges for originator companies, leading to a situation where further development efforts are abandoned. This study concludes that overcoming patent hurdles and formulation limitations, while improving dosage convenience and process simplification, may lead to the possibility of a domestically developed product using indigenous technology.

The use of enteric coating for delayed release

formulations to replicate the absorption of the reference drug with a large surface area pellet formulation was found to be infeasible. However, immediate release formulations showed similar absorption profiles to the reference drug. Pharmacokinetic experiments in beagle dogs showed that dual delayed release is of limited significance if maximum gastrointestinal absorption of dexlansoprazole can be achieved. The 90% confidence intervals for key assessment parameters, AUCt (0.7318-1.1511) and Cmax (0.8117-1.4609), were identified for selected formulation options. Increasing the enteric coating for extended release formulations allowed for a delayed Tmax, slowing the dissipation rate and achieving a formulation equivalent to the reference drug. Therefore, by moving from a pellet to a tablet formulation, dexlansoprazole can improve dosing convenience, simplify the domestic manufacturing process and establish itself as a biologically equivalent product, reducing dependence on imports and encouraging further development.

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