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Original Article

FORMULATION OF LEVOFLOXACIN AS ORODISPERSIBLE TABLETS USING A READY-MADE BLEND OF EXCIPIENTS COMPARED WITH CLASSIC FORMULATION STRATEGIES

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ABSTRACT

Objective: Orodispersible tablets are designed to undergo rapid dispersal when they are placed in the mouth prior to being swallowed. The aim of this study was to compare the performance of a ready-made excipients blend designed for orodispersible tablets with several other conventional methods for the manufacture of tablets using levofloxacin as the active pharmaceutical ingredient.

Methods: Several different formulas were prepared to compare the powder characteristics, and the resulting powders were compressed into tablets using the direct compression method. The result compressed tablets was then evaluated in terms of their physical characteristics and drug release properties.

Results: The results of these experiments showed that the use of ready-made blend provided several advantages over the conventional methods in terms of physical properties of the powders and tablets, as well as their drug release and dissolution properties.

Conclusion: The use of a ready-made powder blend in formulation of ODT of model drug levofloxacin had an advantage over the classic methods of formulation.

Keywords: Orodispersible tablets, Levofloxacin, Prosolv ODT.

INTRODUCTION

Orodispersible tablets (ODTs) are defined as tablets that disperse or disintegrate in less than 1 minute in the mouth prior to being swallowed, which results in the rapid dissolution and absorption of the active pharmaceutical ingredients contained in these tablets, providing a rapid onset of action. ODTs also provide specific advantages to pediatric and geriatric patient populations, which can sometimes experience difficulties in swallowing conventional tablets and capsules [1, 2]. A variety of different processes have been developed for the production of ODTs, including freeze drying and molding, as well as several other more conventional methods, including dry and wet granulation processes and direct compression [3].

The key challenges associated with the formulation of good ODTs include fast disintegration times, reasonably sized tablets, low moisture sensitivity and taste [4]. Given that the major criteria for the formulation of ODTs is a fast disintegration time, tables of this type usually include a large number of disintegrants, such as croscarmellose sodium (CCS or Ac-di-sol®) [5], crospovidone (CP) (Polyplasdone®) [6], sodium starch glycolate (SSG or Primogel®) [7], low-substituted hydroxy propyl cellulose (L-HPC) and pregelatinized starch [8]. Amino acids such as glycine, L-lysine and L-alanine can also be used as oral disintegration accelerators [9].

Ready-made mixtures of pharmaceutical excipients have recently been developed for different types of tablets with the aim of simplifying industrial formulation and tableting processes and reducing the manufacturing costs associated with the production of drugs and pharmaceutical agents.

The aim of this study was to compare the physical characteristics and dissolution properties of ODTs prepared using conventional methods with those prepared using a ready-made mixture of excipients (PROSOLV® ODT). These comparison experiments were conducted using levofloxacin as a model active pharmaceutical ingredient.

MATERIALS AND METHODS

Materials

Levofloxacin powder was kindly provided as a gift by JORIVER Pharmaceuticals (Amman, Jordan). Croscarmellose sodium (CCS or Ac-di-sol®), crospovidone (CP) (Polyplasdone®), sodium starch glycolate (SSG or Primogel®), mannitol, Acecil®, aspartame, talc, magnesium stearate and prosolv® ODT were kindly provided as gifts by HIKMA Pharmaceuticals (Amman, Jordan). Concentrated hydrochloric acid (37%) was purchased from Biosolve chimie SARL (Dieuze, France)

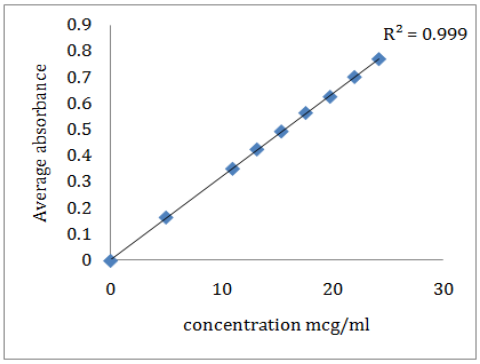

Fig. 1: Calibration curve for levofloxacin in 0.1 N HCl at 37±0.5 °C

Methods

Levofloxacin: method of analysis and calibration curve

As recommended by the International Conference on Harmonization (ICH) guidelines, the linearity of an analytical method should be determined using at least five different concentrations over a specified range of concentrations. In the experiments conducted in the current study, the linearity was determined by testing eight different concentrations of Levofloxacin in the range of 5–24.2 µg/ml (i.e., 5, 11, 13.2, 15.4, 17.6, 19.8, 22 and 24.2), with each individual concentration being tested in triplicate. The response at each concentration was represented by the UV absorbance, which was determined using a Jasco V 530 spectrophotometer (Jasco, Tokyo, Japan) with a λ_{max} value of 293 nm. The average absorbance values were plotted against concentration, and the results were subjected to the least square regression analysis, as shown in fig. 1.

Formulation of Levofloxacin ODT

Levofloxacin ODTs were prepared using a direct compression method. Six different formulas were prepared. The first three formulas (F1–F3) were prepared using a classic formulation strategy based on three different disintegrants, including CCS, SSG and CP, which were all added at a concentration of 5% (w/w) per tablet. All three formulas contained the same amount of mannitol, which was used as a diluent. The amounts of all of the other ingredients were also kept the same to avoid any variability across the different formulas. Formulas F4 and F5 were prepared based on the preliminary results for the evaluation of formulas F1–F3. For F4, the concentration of CCS was increased to 7% (w/w). Avicel® was added as an extra diluent to F5 and the concentration of CCS was also increased to 7% (w/w). F 6 was prepared using a ready-made ODT blend of excipients (i.e., PROSOLV® ODT), which contains microcrystalline cellulose, colloidal silicon dioxide, mannitol, fructose and CP. The contents of each formula are listed in table 1.

All of the powder formulas were sieved through a 60 micron mesh sieves, and the resulting powders were collected and subjected to numerous pre-compression tests, including bulk density, tapped density, angle of repose, percentage compressibility and Hausner ratio analyses. The formulas were then compressed using a 10 mm flat surface circular punch on a rotary tablet press (Cadmach® compression machine, Ahmedabad, India).

Table 1: Formulation design

Ingredients	F1 (mg)	F2 (mg)	F3 (mg)	F4 (mg)	F5 (mg)	F6 (mg)
Levofloxacin	250	250	250	250	250	250
CCS	25	-	-	35	35	-
SSG	-	25	-	-	-	-
CP	-	-	25	-	-	-
Aspartame	5	5	5	5	5	-
Talc	8	8	8	8	8	-
Mannitol	209	209	209	199	149	-
Avicel	-	-	-	-	50	-
Prosolv® ODT	-	-	-	-	-	247
Mg stearate	3	3	3	3	3	3
Total (mg)	500	500	500	500	500	500

Evaluation of the tablets

The tablets prepared in the current study were evaluated against a variety of official and unofficial specifications.

Weight Variation: Twenty tablets were randomly selected from each batch to determine the average weight properties of the tablets. The individual tablets were then weighed, and their individual weights were compared with the average weight [9].

Hardness and Friability: These properties were determined according to the procedure described in the 2009 edition of the United States Pharmacopeia (USP). The tablets were evaluated in terms of hardness using an MA-35 electrical hardness tester (Pharma Test, Hainburg, Germany). The friability properties of the tablets were tested using a PTF 10E friabilator (Pharma Test) [10, 11].

Content Uniformity Test: Twenty of the tablets prepared in the current study were accurately weighed and ground into a fine powder using a pestle and mortar. A weighed portion of each powder equivalent to 1 mg/ml of prepared tablet was then transferred in to a volumetric flask and the drug was extracted using methanol as the solvent. The contents of the flask were then sonicated for 10 min and diluted with a 0.1 N HCl solution. The resulting solutions were then analyzed using a UV spectrophotometer at 293 nm [12].

Wetting time

The wetting time is closely related to the inner structure of the tablets and the hydrophilicity of the excipients. A piece of tissue paper was folded over on itself and then folded again before being placed in a Petri dish containing 6 mL of water. A tablet was then placed on top of the folded paper and the time taken for the complete wetting of the tablet was measured in seconds [13].

***In vitro* disintegration time**

In vitro disintegration time was determined using a VDT 3 disintegration test apparatus (Lasany International, Panchkula, India). A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time taken for the complete disintegration of the tablet with no palatable mass remaining in the apparatus was measured in seconds [14].

***In vitro* drug dissolution**

The dissolution of levofloxacin from the prepared tablets was evaluated according to US FDA 2013 document, using the rotating basket method (apparatus 1) described in the USP. The basket rotation speed was set at 100 rpm. A 0.1 N HCl solution was used as the dissolution media, with six tablets being tested each time in 900 mL of dissolution media. A thermostat was used to control the temperature of the immersion fluid in the range of 37±0.5 °C. Ten milliliter aliquots of the filtered material were manually withdrawn at pre-determined time intervals (i.e., 2, 5, 10, 20, 30 and 45 min) and replaced with 10 mL of fresh media, which had been maintained at the same temperature. The concentration of the drug was measured after proper dilution using a UV spectrophotometer with a λmax value of 293 nm.

Drug dissolution processes were conducted for the six formulas prepared in the current study and the amount of drug dissolved in each sample was plotted against the time in minutes.

RESULTS AND DISCUSSION

The results of the pre-compression studies for the different powder blends of the six formulas showed prepared in the current study showed that they all possessed acceptable physical characteristics and flow properties (table 2). The use of talc as a glidant had a positive impact on the flowability properties of the powder blends of formulas F1–F5. However, the use of the ready-made mixture (Prosolv ODT) in F6 had a much greater impact on the flow properties of this material, as demonstrated by the angle of repose (23 °), percentage compressibility (8.93%) and Hausner ratio (1.09) values of this material, which were the lowest of all of the powders tested in the current study [1].

With regard to the physical characteristics of the compressed tablets, the hardness and friability values of the six different formulas were all very close to each other, and well within the acceptable range required for ODTs [15].

The wetting time refers to the ability of a tablets inner structure to absorb water to facilitate the disintegration process in the mouth. Avicel had been reported to facilitate the adsorption of water through capillary action when it is added during the formulation of tablets [16]. Formula F5, which contained a 1:3 (w/w) mixture of Avicel and mannitol, gave a shorter disintegration time than formulas F1–F3. However, increasing the amount of disintegrant (CCS) from 5 to 7% also resulted in a decrease in the disintegration time. A good correlation was observed between the wetting time and the disintegration, which indicated that there was a good correlation between the water absorption capacity measured by the wetting time and the *in vitro* disintegration time of the tablets. Formula F6, which was made with the ready-made excipient blend, gave very low wetting and disintegration times, which are good characteristics for ODTs.

A comparison of the results obtained for formulas F1–F3, which contained three different types of disintegrants, is shown in table 3. These results revealed that formula F1, which contained CCS as a disintegrant, gave the shortest wetting and disintegration times of these three formulas. However, all results are accepted for ODT. Increasing the concentration of CCS from 5 to 7% (w/w) led to a decrease in the wetting and disintegration times. From an economical perspective, the use of a ready-made mixture of excipients would be preferable to the use of a larger loading of CSS.

Table 2: Micrometric properties of the different powder blends

Formula code	F1	F2	F3	F4	F5	F6
Bulk density (gm/ml)	0.48	0.47	0.49	0.48	0.58	0.51
Tapped Density (gm/ml)	0.55	0.54	0.55	0.56	0.66	0.56
Angle of Repose Θ	28°	27°	30°	27°	25°	23°
Percentage compressibility	12.72	12.69	10.90	14.2	12.12	8.93
Hausner Ratio	1.14	1.15	1.12	1.16	1.13	1.09

Table 3: Evaluation of the tablets

Formula code	Weight variation	Hardness* (Kg/cm2)	Friability* (%)	Wetting time* (sec)	*In vitro* disintegration time* (sec)	Drug content* (%)
F1	pass	3.5±0.51	0.61±0.05	38±1.1	40±1.3	98±1.5
F2	pass	3.6±0.62	0.60±0.06	48±1.5	45±2.1	99±2.0
F3	pass	3.4±0.38	0.63±0.09	45±2.0	48±2.0	100±1.1
F4	pass	3.5±0.44	0.55±0.09	29±1.8	32±1.2	101±0.98
F5	pass	3.7±0.51	0.52±0.08	35±2.1	36±3.1	98±0.99
F6	pass	3.2±0.08	0.40±0.01	30±1.5	31±1.3	99±0.5

* All values are expressed as mean±SD

Table 4: Comparison of the amount of drug dissolved in 5 min ($T_{5\ min}$) for the six different formulas prepared in the current study

Formula code	F1	F2	F3	F4	F5	F6
Percent drug dissolved	25±2.0	24±1.8	24±1.2	28±1.9	22±2.0	37±1.6

Examining the dissolution study of the six formulas in 0.1 N HCl, results showed that there were no big differences between the releases of levofloxacin from the prepared formulas. A comparison of the amount of drug released after 5 min from the six different formulas prepared in the current study (table 4), revealed that F6, which was prepared using PROSOLV® ODT, showed the highest level of drug release of all of the formulas tested. This result indicated that F6 allowed for the fast and efficient release of the drug from the tablet, which would be necessary for an ODT.

An evaluation of the cost effectiveness of the different formulas revealed that the use of a ready-made blend was much more cost effective for the mass production of levofloxacin tablets for immediate oral release.

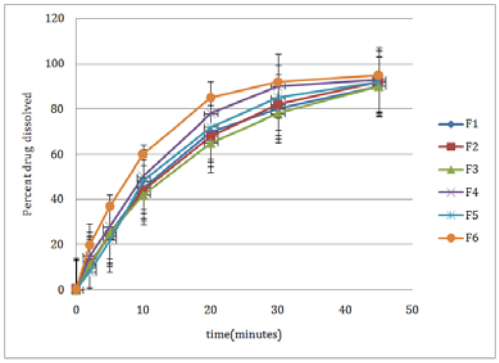

Fig. 2: Dissolution profile of levofloxacin in the six prepared formulas in 0.1 N HCl and 37 °C (n=3)

CONCLUSION

The use of a ready-made powder blend of excipients for the formulation of a levofloxacin ODT for immediate oral release led to improved pre-compression physical characteristics in the powdered formulas, as well as improvements in the physical characteristics, drug dissolution rates and cost effectiveness of the corresponding compressed tablets.

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ABBREVIATION

ODT (orodispersible tablets), CCS (Croscarmellose sodium), CP (Crospovidone), SSG (Sodium starch glycolate).

CONFLICT OF INTERESTS

Declared None

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