Preparation and evaluation of ibuprofen gels: Effect of different variables

ABSTRACT

Introduction: Ibuprofen is a potent nonsteroidal anti-inflammatory (NSAID) drug. Its poor solubility and gastric irritation in oral forms represent a great challenge to overcome these problems.

Objective: Solid dispersion incorporated gel approach aims at enhancing dissolution rate and decreasing ibuprofen related adverse effects through transdermal delivery as an alternative to oral administration.

Methods: Ibuprofen solid dispersions were prepared by fusion of drug: polyethylene glycol 6000 (PEG_{6000}) in ratios 1:1and 1:2. The prepared solid dispersions were evaluated for dissolution. Depending on dissolution study, solid dispersion of ibuprofen: PEG 6000 prepared in 1:2 ratio was selected, incorporated into different gel bases [Methyl Cellulose (MC), Hydroxy Propyl Methyl Cellulose (HPMC) and Carbapol 940] and compared with marketed Ibuprofen gel (Profinal® gel).

Results: The release of Ibuprofen after 60 min from Ibuprofen solid dispersions was 94.89%, 86.30% while the release of pure drug after the same time was 10.45 %. The marketed gel (Profinal® gel) showed a highest dissolution than solid dispersion incorporated gels.

Conclusion: Solid dispersion of Ibuprofen with PEG 6000 increased the dissolution and skin permeability of Ibuprofen but less therapeutic effective than the marketed gel (Profinal® gel).

Keywords: Ibuprofen, Solid dispersion, Transdermal delivery, Profinal® gel.

INTRODUCTION

Ibuprofen [2-(4-isobutylphenyl) propionic acid] is a potent nonsteroidal anti-inflammatory (NSAID) drug that is often used for the treatment of acute and chronic arthritic conditions [1]. Since dissolution is the rate-limiting step during drug absorption, the poor water solubility of ibuprofen in oral forms results in low bioavailability due to erratic or incomplete absorption from the gastrointestinal tract [2, 3]. In addition to absorption difficulties, oral formulations of ibuprofen can cause gastric mucosal damage, which may result in ulceration and bleeding. The current approaches aim at decreasing ibuprofen related adverse effects through transdermal delivery as an alternative to oral administration [4, 5]. One of the biggest challenges in developing an effective transdermal drug delivery system (TDDS) is the transfer of the drug through the tightly structured stratum corneum since the stratum corneum is the outermost barrier of body and most of agents have low permeability through it [6]. Transdermal delivery of drugs involves two consecutive processes: the release of the drug from the topical formulation, and its absorption into the skin at the site of application [7]. Increasing the release rate of the drug from the dosage form improves transdermal delivery of drugs [8, 9, 10]. Solid dispersion technique can be used to improve dissolution of poorly water-soluble drugs such as ibuprofen [11, 12]. Various polymers such as polyvinylpyrrolidone (PVP) [13, 14], HPMC [15], ethylcellulose [16] and polyethylene glycol (PEG) [14, 18] are common polymeric carriers in such systems [19]. Transdermal formulation like gel, ointment, cream, patches and lotion are available but out of these gels is preferred due to its better application property and better percutaneous absorption [20]. Solid

dispersion incorporated gel is the better approach to enhance the in vitro topical permeation [21].

The objective of this study was to use solid dispersion incorporated gel approach for enhancing transdermal delivery of ibuprofen and then comparing the in vitro release results of the formulated gel and branded gel (Profinal® gel).

MATERIALS AND METHODS

MATERIALS

Ibuprofen (gift sample); PEG 6000 was purchased from Merck company (Germany); Methyl Cellulose powder (MC) and Hydroxypropyl Methyl Cellulose powder (HPMC) were purchased from Sigma Aldrich (Germany); Carbopol 940 was obtained from Goodrich Chemical Company (England); Sodium hydroxide, Disodium hydrogen phosphate, and potassium dihydrogen phosphate were purchased from Sigma Chemical Company (USA). All other chemicals and solvents were of analytical grade.

METHODS

Preparation of ibuprofen solid dispersion by melting method

Ibuprofen: PEG 6000 solid dispersions (1:1 and 1:2 ratios), were mixed, melted and solidified the dispersion by cooling on an ice bath under vigorous stirring and the final solid mass was crushed, pulverized to a powder and passed through sieve mesh no. 35. There was not interaction between Ibuprofen and PEG 6000 from the previous literature [21].

In vitro release study

In-vitro release of pure Ibuprofen and Ibuprofen from the prepared solid dispersions was carried out in phosphate buffer solution (900 ml, pH 7.4) at 37±0.5^{0}C and 100 rpm using a USP I dissolution apparatus (Erweka TD6R, Germany [22]. At predetermined time intervals (5, 10, 15, 30, 45 and 60 min), aliquots of one milliliter of the release medium were withdrawn and diluted with 9ml of phosphate buffer solution PH= 7.4 then filtered for analysis and replaced with equal volume of the buffer solution to maintain a constant volume. The absorbance of the collected samples was measured using Ultraviolet spectrophotometer (Jenway 6305 uv/vis, UK) at λ_{max} of 222nm. The in vitro release results were illustrated in table (1) and figure (1). The release data were subjected to kinetic analysis according to zero, first, Higuchi diffusion models [23], Hixson-Crowell cup root law [24] and Baker-Lonsdale equation [25]. The correlation coefficient (r), the order of release pattern and $t_{50\%}$value was determined and listed in table (2).

Selection of gel bases

The least concentration of methyl cellulose (3%), hydroxyl propyl methyl cellulose (3%) and Carbopol 940 (0.5%) was selected since the least concentration of these bases gave the best release with most previously studied drugs and it is apparent that the gel and drug release rates decrease as the gel concentration increased [26-30].

Preparation of plain gel bases

The weighed amount of gelling agents was sprinkled gently using magnetic stirrer in 100 ml beaker containing boiling distilled water (in case of MC and HPMC) or distilled water (in case of Carbopol 940). Stirring was continued until a thin hazy dispersion, without lumps, was

formed. Leaving over night in the refrigerator may be necessary for complete gel dispersion [31].

Preparation of Ibuprofen gels

Depending on dissolution study, solid dispersion of Ibuprofen with PEG 6000 (1:2) was selected. The amount of solid dispersion equivalent to 5 gm of drug was dissolved in distilled water at 5-10^{o}C and mixed with gel while liquid.

Physical investigation of Ibuprofen gels

The prepared Ibuprofen gels were tested for their color, odor and homogeneity.

In-vitro release of Ibuprofen from different gels

In-vitro release of Ibuprofen from the prepared gels and marketed gel (Profinal® gel) was carried out in phosphate buffer solution (900 ml, pH 7.4) at 32±0.5^{0}C and 50 rpm using a modified USP I dissolution apparatus. At predetermined time intervals 30, 60, 90, 120, 150 and 180 min), aliquots of one milliliter of the release medium were withdrawn and diluted with 9 ml of phosphate buffer solution PH= 7.4 then filtered for analysis and replaced with equal volume of the buffer solution to maintain a constant volume. The absorbance of the collected samples was measured spectrophotometrically at λ_{max} of 222nm. The release results were illustrated in table (3) and figure (2). The kinetic analysis of all release data were also calculated and listed in table (4).

RESULTS AND DISCUSSION

In this study, we used a solid dispersion technique to design a topical formulation of Ibuprofen since several studies have shown that solid

dispersion technique increases the permeability through stratum corneum [32].

We found that solid dispersion technique has improved the dissolution of Ibuprofen and the drug release % increased as the ratio of drug: polymer increased from 1:1 to 1:2 as shown in table 1 and figure 1. Accordingly, Ibuprofen: PEG 6000 solid dispersion formulation (1:2) was chosen for further preparation of Ibuprofen gels.

Table (1): In vitro release of Ibuprofen and Ibuprofen from solid dispersions

Time	Ibuprofen release %		
	Ibuprofen	Ibuprofen: PEG 6000 (1:1)	Ibuprofen: PEG 6000 (1:2)
0	0	0	0
5	8.21	34.26	40.63
10	8.35	46.87	54.93
15	8.61	55.92	68.04
30	9.03	63.43	78
45	9.64	76.41	82.83
60	10.45	86.30	94.89

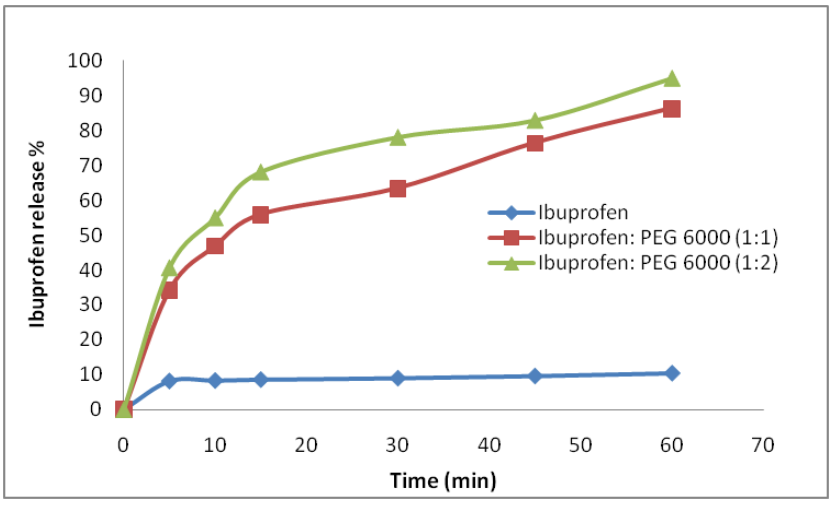

Figure (1): In vitro release profiles of Ibuprofen and Ibuprofen solid dispersions

The best kinetic order was calculated from the highest values of the obtained correlation coefficients. The kinetic analysis of all release profiles followed diffusion controlled mechanism as shown in table (2).

Table (2): Kinetic analysis of the release data of* Ibuprofen from *the prepared solid dispersions

Formulations	Model	R	K	$t_{1/2}$	Order
Ibuprofen	**Zero-order** **First-order** **Second-order** **diffusion model** **H-C** **B-L**	0.767 0.608 0.629 <u>0.911</u> 0.711 0.878	0.249 0.096 0.000 1.702 0.004 4.89	200.63 7.21 41.26 862.59 238.50 1124.91	**Diffusion**
Ibuprofen : PEG 6000 (1:1)	**Zero-order** **First-order** **Second-order** **diffusion model** **H-C** **B-L**	0.965 0.290 0.928 <u>0.996</u> 0.988 0.963	2.569 0.038 0.002 15.246 0.068 0.007	19.45 17.86 4.96 10.75 14.05 7.35	**Diffusion**
Ibuprofen : PEG 6000 (1:2)	**Zero-order** **First-order** **Second-order** **diffusion model** **H-C** **B-L**	0.946 0.091 0.812 <u>0.998</u> 0.986 0.970	2.801 0.012 0.004 16.980 0.086 0.010	17.85 57.22 2.01 8.66 11.01 5.18	**Diffusion**

We also found that the physical investigation of the prepared gels showed a good texture, homogeneity and ease of spreading, with weight milky color colloidal dispersions.

From table (3) and figure (2), The Ibuprofen % release from different gels can be arranged in descending order as follows: The marketed gel (Profinal® gel) > Solid dispersion incorporated MC gel base > Solid dispersion incorporated MC gel base > Solid dispersion incorporated HPMC gel base> Solid dispersion incorporated Carbapol 940 gel base**.** The kinetic analysis of all release profiles followed diffusion controlled mechanism as shown in table (3).

Table (2): In vitro release of Ibuprofen from different gels

Time	Ibuprofen release %			
	Profinal® gel	MC gel base	HPMC gel base	Carbapol 940 gel base
0	0	0	0	0
30	39.7	23.9	16.20	11.6
60	53.5	33.6	25.3	21.8
90	65.2	41.8	36.4	30.4
120	72.9	48.4	44.2	35.6
150	82.8	52.2	48.3	40.6
180	88.7	60.5	54.8	45.2

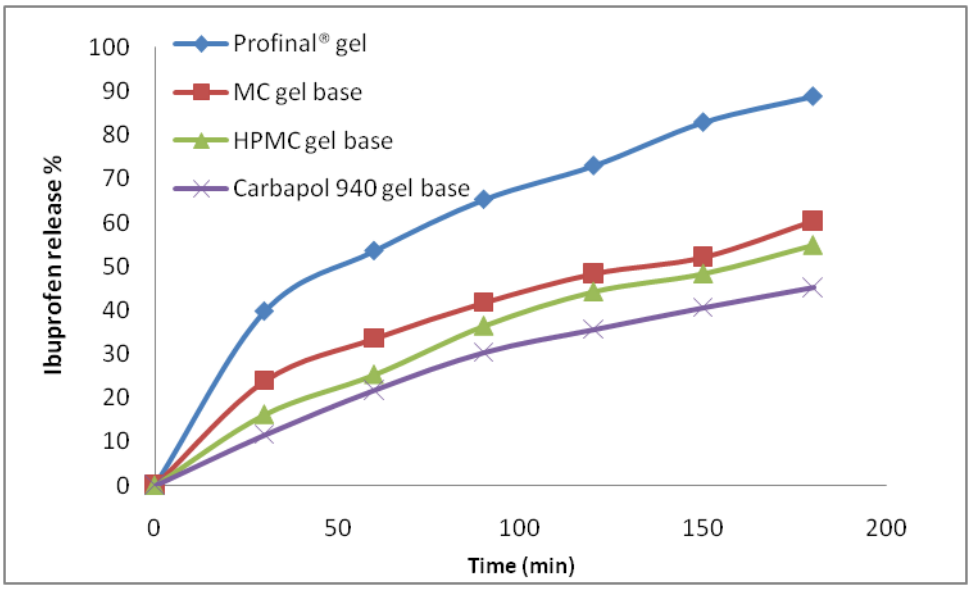

Figure (2): In vitro release profiles of Ibuprofen from different gels

Table (3): Kinetic analysis of the release data of Ibuprofen from different gels

Formulations	Model	R	K	$t_{1/2}$	Order
Profinal® gel	**Zero-order**	0.942	0.4420.	112.99	**Diffusion**
	First-order	0.133	00.003	190.90	
	Second-order	0.367	0.001	85.27	
	diffusion model	0.998	6.699	57.40	
	H-C	0.319	0.003	245.44	
	B-L	0.425	0.000	107.35	
MC gel base containing solid dispersion	**Zero-order**	0.958	0.301	166.07	**Diffusion**
	First-order	0.045	0.001	492.30	
	Second-order	0.175	2.37	422.54	
	diffusion model	0.998	4.418	128.03	
	H-C	0.288	0.001	520.37	
	B-L	0.409	0.000	357.48	
HPMC gel base containing solid dispersion	**Zero-order**	0.981	0.294	169.69	**Diffusion**
	First-order	0.047	0.001	462.77	
	Second-order	0.185	2.305	434.04	
	diffusion model	0.990	4.185	142.67	
	H-C	0.350	0.002	474.78	
	B-L	0.445	0.001	380.80	
Carbapol 940 gel base containing solid dispersion	**Zero-order**	0.982	0.246	202.50	**Diffusion**
	First-order	0.036	0.001	588.30	
	Second-order	0.148	1.640	609.32	
	diffusion model	0.998	3.497	204.34	
	H-C	0.354	0.001	584.63	
	B-L	0.457	9.520	577.48	

CONCLUSION

Solid dispersion of Ibuprofen with PEG 6000 increased the dissolution of ibuprofen and the effect depends on the drug/polymer weight ratio. Highest dissolution of Ibuprofen was achieved at drug/polymer ratio 1:2. Additionally, Ibuprofen solid dispersion is a better alternative to improve penetration through the skin. The data suggested that the marketed gel (Profinal® gel) showed a highest dissolution than solid dispersion incorporated gels.

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