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In Vitro Formulation and Evaluation of Diclofenac Sodium Buccal Tablet for the Treatment of Local Pain and Inflammation

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Abstract: *The use of polymeric materials receives more attention in the development of drug delivery as they aid in controlling the release of drugs to the site of action. The aim of this formulation is to develop a suitable diclofenac buccal tablet that releases their drugs through buccal mucosal membrane lining in a cheek in order to evaluate the compatibility of the excipient used in the formulation. The tablets were prepared by direct compression using excipients which include hydroxyl propyl methyl cellulose (HPMC), sorbitol, magnesium stearate and diclofenac as API. A good dissolution has been recorded due to a constant release of drug for up to 60 minute dissolution time. However, an average value of compressibility index and Hausner ratio emerged within the range of 31.88 and 1.47 respectively, which indicates very poor flow character based on the scale of followability. Friability was also carried out using friability tester with the view to ascertain the hardness of the tablets but the formulation percentage loss was found to be greater than1.0% percent indicating a poor performance. Based on the result, it seems the powder was not subjected to granulation processing therefore subjection of powder to granulation processing is recommended in a further research.*

Keywords*: Buccal tablet, Diclofenac sodium, Inflammation disease, Lining & Mucoadhensive*

Introduction

Tissue injury is one of the primary causes of inflammation and inflammatory pain that are accompanied with temporomandibular joint disorder, arthritis, lower back injury, and surgery. (Ji *et al.,* 2011). These diseases usually occur due to tissue damage that causes dilation of venules, increase in vascular permeability, infiltration of histamine, cytokine and other inflammatory components (Brin Mohan *et al*., 2012). The inflammatory response often accompanies with the development of neuropathic pain, which lead to extensive chronic pain (White *et al.,* 2015). The study reported that around 11 to 24% of the world population suffers from chronic muscle pain, with the majority experienced musculoskeletal pain. Musculoskeletal pain is a deadly disease which results in reduced function and sometimes causes significant disability (Sluka and Nicholas, 2015). When it persist it lead to long lasting pain and other disability, such rheumatoid arthritis. Rheumatoid arthritis (RA) it a diseases associated with

chronic inflammatory autoimmune disease, it's substantially determined by developments of genetic factors that are likely to account for 50% to 60% of disease susceptibility (Tong *et al*., 2013). It however characterized by pain swelling, stiffness and damage of joints due to synovial inflammation and effusion. RA synovitis has a higher tendency to disobey tissue boundaries, because of infiltrating articular bone and cartilage, which usually cause loss of working ability and early retirement, premature death, if not treated properly (Josef *et al.,* 2007). Therefore; pain and inflammation irrespective of whether it's acute or chronic, it contains inflammatory profile consisting mediator that present in the pain syndrome. This biochemical mediator of inflammation includes cytokines, neurotransmitter, and neuropeptides, peripheral and central pain, nociceptive or neuropathic pain. The inflammatory profile may differ from one person to another and may have variation at a different time within the same person. Therefore, treatment of the pain disorder it has to do with the understanding inflammatory profile and can either be treated medically or surgically (Omoiqui, 2007).

However sustained drug release delivery system, is an essential tool for improving therapeutic effect, by decreasing side effects and minimizing the bioavailability of conventional drugs, a buccal tablet is one of easiest administration of sustained release tablet, this type of drug are typically formulated with hydrophilic polymers that include the hydroxylpropyl because of the acid hydrolysis and hepatic first pass effect (Salamat *et al*.,2005). Buccal administration is found to be safer ways of drugs application because absorption of drugs can be terminated by removing the dosage form from the buccal cavity when toxicity arise (Raju *et al*., 2011).

Buccal Tablets contains certain properties in the mucosa, such as maintaining its position in the mouth for a few hours, release the drug in a controlled manner and gives the drug release in a unidirectional way towards the mucosa. It found to be strong adhesive contact to the mucosa; the systems have to be stable adhesiveness and impermeable backing layer (Aditya *et al*., 2010).

Table 1 excipients use in the formulation and their respective quantity

Formulation	Diclofenac (g)	Glucose (g)		Sorbitol (g)	HPMC (g)
A	5.5	0.55	-	3.87	10
B	5.5	1.66	-	2.76	10
C	5.5	-	0.55	3.87	10
D	5.5	-	1.66	2.76	10

2.0 Materials and Methods

2.1 Materials

The materials used in the formulation were diclofenac sodium salt as the API (alfa easer) hydro propyl methyl cellulose (HPMC) as the mucoadhesive polymer and binder (Sigma- Aldrich UK) magnesium stearate as the glidant (Sigma –Aldrich) glucose (Sigma-Aldrich UK), and sorbitol (Sigma-Aldrich UK).

2.2 Methods

2.2.1 In vitro disintegration studies

The disintegration was conducted using disintegration tester (variant 100) consist of basket-rack assembly with 1 liter, of water. Low form beaker 149 +/- 11 mm height and 106 +/- 9 mm inside diameter, for the immersion fluid at constant frequency rate between 29 and 36 cycles per minute through a distance of 55+/- 6mm. One tablet was inserted in each of the six tubes of the basket, and each tube had a transparent plastic disc placed within it, 9.5+/- 0.15mm thick and 60.7+/-15 in diameter. The apparatus was operating at specified medium, at the temperature of 37 +- 2 and disintegration time was determined by visual observation up 15 minutes. The analysis was carried out in triplicate for each of sample A, B and D (Appendix XIIA Disintegration BPa., 2015).

2.3 Powder Flow

The followability test was used analyses using powder flow machine (ERWEKA Germany) to determine the flow the divided solid powder and granules. 10 g of each formulation was used to measure the ability of the powder to overcome the cohesion and friction to flow through an orifice; the device is composed of a Stainless steel funnel and disks. There is an orifice by a lever the samples was gently put into the container and allow to settle for 30 seconds (Huang et al., 2014). The sample was introduced individually without compacting the sample weight. Each formulation was separately introduced, and the device was closed. When testing the device was activated, presenting an opening where the sample would flow out of the funnel and results were recorded (Appendix XII N. powder flow BPb, 2015).

2.3.1 Angle of repose

The angle of repose has been used for several analytical sciences to describe the flow properties of the solid powder. The angle of repose was determined in the powder flow tester (GTB, E rweka, Germany). The flow time and angle of response can be determined by draining the sample through a funnel located at a predefined height above the circular plate. Three different diameters were recorded; thus 10mm, 15mm, and 25mm. Each of the samples was measured in with three apertures, and average value was taken et the end (Sarraguca *et al*., 2010)

2.3.1Tapped density

Tap density was achieved by mechanical tapping. The powder was placed into a measuring cylinder which was part of the tap densitometer (variant vk 200), 10ml of each of the formulation A, B, C and D were weight into a 100 ml measuring cylinder. The weight of the

powder was mechanically tapped in a measuring cylinder using tap density tester. The instrument was set to 10, 500 and 1250 respectively, an initial and final volume of each of the formulation were recorded (Appendix XII D. BPc., 2015). Powder tap density was used to calculate the compressibility and Hausner ratio. This can be calculated according to the following equation:

Hausner ratio= (powder tapped)/(p
tapped) (equation 1a) (Appendix XII D.
BPc., 2015).
CI = X 100) (equation 1b) (kaialy *et al.,* 2014).

2.4 Hardiness Test

Hardness was analysed to determine the resistance of a tablet to chipping, abrasion or breakage in the process of transportation and handling before its usage. Hardness testing is a vital parameter in pharmaceutical industries because it can affect dissolution and disintegration time (Chowdhury *et al.,* 2015). The test was conducted using tablet hardness tester (VK 7 Varian 200 UK) the apparatus consist of six jaws opposite to each other. Tablets were measured by placing the tablet between the jaws, for each tablet the measurement was performed in the same way on direction of the application. Ten tablets were used for each determination, and any fragment of the tablet will be removed (Appendix VII H. BPd., 2015).

2.4.1 Friability

Determination of friability was conducted by weighing a randomly chosen ten tablets which were dedusted before testing. The drum was attached to the horizontal axis of the device and rotated at 25 +/- 1 rpm per minute. The tablet of each of the formulation was weight and placed into the drum, and the drum was rotated at 25 rpm in 1 minute as stated in Appendix XII G. BP, 2014. The drum was to rotate 100 times in four minutes; then the tablet was removed from the drum; all loose dust was removed from the tablet and weight again (Appendix XVII-G, BPe, 2015). The percentage friability can be calculated using the following equation

% friability = (initial weight – final weight)/(initial weight) x100 (Kumar and Babu., 2014).

2.4.2 Crushing strength

The crushing strength of the tablet was determined by using the hardness tester, tablets were placed between the jaws of the Monsanto hardness tester on its edge, and then force was applied (Chowdhury *et al.,* 2015). Ten tablets were analysed, and each tablet was orientated in the same direction of application of the force. The crushing strength that caused the tablet to break was recorded (Zieffels and steckel, 2010) Kp value recorded were converted to Newton according to below equation

Newton = Kp x 9.80665 (Appendix XII H. BPf, 2015).

3.0 Result and Discussion

3.1 In vitro disintegration profile

Disintegration is the measurement of the quality control of the tablet formulation;

disintegrating testers determine how the tablet disintegrates within the prescribed time according to British Pharmacopeia (BP). Six tablets of each of the formulation A, B, C and D in figure 1a, were analysed in three replicate in vitro disintegration using demineralised water, medium, the tablet set for disintegration. Formulations A was first analysed and observe visually, during the disintegration test the tablet would occasionally stick to the beaker or the disk, the tablets did not disintegrate within the 15 minutes of the specified time of British Pharmacopeia. All the three sets of formulation A showed the same behaviour during disintegration. The same method was used for formulation B, C, and D; all the formulation refused to disintegrate within the British Pharmacopeia specified time. This implies that the formulation is a good buccal tablet of diclofenac sodium because it does obey the 15 minute disintegration time for uncoated tablet prescribed by British Pharmacopeia because buccal do not require to disintegrate within a short period of 15minute. Therefore all the formulation is good for the sustained release tablet; therefore, it can give efficient drug delivery into mucosa lining cheek. These could be due to the amount of API in the formulation and excipient like HPMC and sorbitol that give hard tablet when compressed with higher pressure. Because reaction hydroxyl propyl methylcellulose (HPMC), with diclofenac sodium it gives well-sustained release and compression of tablets with higher pressure, give hard tablet that can take time before it disintegrates. These correspond to the literature by Donauer and Lobenberg, (2007) if the tablet was compressed under low compression the tablet will disintegrate very quickly, and when it ware compressed with higher pressure, the table will not disintegrate within very short periods of time.

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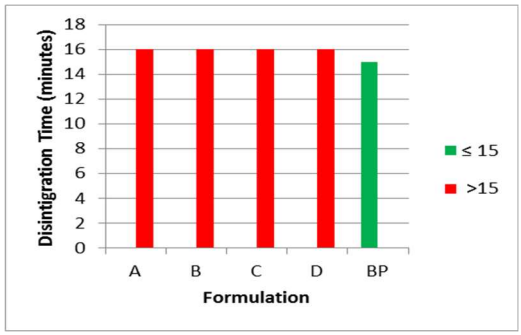

Figure 1a tablet disintegration Profile

3.1.1 *In vitro diclofenac dissolution*

The drug release patterns of all the formulation A to D, for up 60 minutes are given in figure 1b. The drug release pattern of the in vitro dissolution data of diclofenac buccal tablet of all the formulation had a similar release pattern. The drug begins to release from the second minute and rapidly increased the release of the drug until the tenth minute. Then, the constant releases of the drug continue up to sixty minutes. All tablets were fully dissolved within the testing time which was 60 minutes. A calibration curve was prepared by mixing 50mg of Diclofenac powder with 50mL of distilled water, collected and diluted with three set of ten tubes. All the tubes were tested by UV-VIS at 276 nm, and a calibration curve data was obtained and then plotted. However from the calibration curve, the straight equation and gradient are found to be (y=0.5865x-0.0111) and (R2= 1) respectively. The concentration of diclofenac at each time interval was obtained. Therefore, we conclude that the formulation is good because it gives constant release of the drug. The reason for the constant release of drug in this formulation was due to the interaction between sodium diclofenac and HPMC polymer. Because buccal tablet formulation with a mixture of sodium diclofenac and HPMC give greater bio adhesive, as observe in figure 1b, the more the polymer increase, the more the mucoadhesive strength increase. This is in line with literature Velmurugan *et al.,* (2010) the release of a buccal tablet could be ruled by the amount of polymer content in the formulation because as the concentration of polymer (HPMC) increase the rate of release will slow down. These increases the proportion of polymer matrix and also increase the amount of water uptake which results to greater swelling leading to a thicker gel layer with the longer diffusional path. The controlled drug delivery systems must deliver the drugs at predetermined rate, duration and location in the body to achieve an optimum drug level blood concentration (Aditya *et al.,* 2010). The important of controlled drug- delivery system are to ensure safety and

to improve efficacy as well as to improve patient compliance, hydrophilic tablets swell upon ingestion and a gel layer for tablet surface, the gel layer, however, retard further ingress of fluid and subsequent drug release (Singhvi and Singh, 2011).

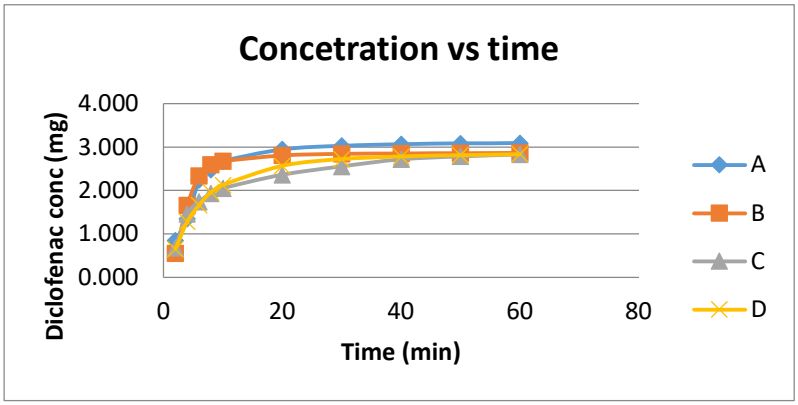

Figure 1b, tablet dissolution

3.2 *Tapped density and followability*

In figure 2a, The compressibility index and Hausner ratio of the formulation A were 32.77 and 1.49, comparing the compressibility and Hausner ratio of the scale followability according to British Pharmacopeia, the result obtained in the formulation A fell within the range of very poor. For the formulations B and C, the values obtained for the compressibility and Hausner ratio figure 2a, also fall within the range of very poor on a scale of followability. The compressibility index and Hausner ratio of formulation D were 28.41 and 1.4, by comparing the scale of followability the value was within the range of poor. This indicates that the values obtained for all formulations in figure 2a failed the test according to British Pharmacopeia. This indicated that all the formulation did not flow through the machine correctly, and excipients and API are not properly mixed, as there were different amounts of each excipient in each formulation. Powder flow plays a significant role in a pharmaceutical development process; poor powder flow can lead variation in tablet weight, poor uniformity content can lead to irregular tablet properties, such as disintegration time, sometimes dissolution rates and breaking strength (Sun,2010). This was attributed to the surface area, particle shape and size distribution of the blend as well of the moisture content of the API, which increases the cohesiveness of the particle of the blend. Considering the Hausner ratios and compressibility index of the excipient and API used in this formulation, all fall within the range of passable and very, very poor. Only sorbitol fall with the range of good in a formulation in figure 2b, this in line with literature Huang *et al.,* (2015). Poor followability of pharmaceutical powders can be attributed to many factors; these include humidity, particle shape, particle size distribution for instance fine pharmaceutical ingredients. APIs are very cohesive and have poor followability because fine particles experience a strong inter-particle force, which exceeds the weight of the particles, quantified by their ratio denoted by the granular bond number. Consequently, pharmaceutical blends consisting of excellent APIs usually have processing issues at high API

doses, may formulations suffer from poor content uniformity at low API doses because of their poor followability and presence of API agglomerates. To improve followability in this regard, the powders need to be subjected to granulation processing; the powders should be micronized to produce particles with pre-determined properties using spray drying (Kaialy and Nokhodchi, 2013)

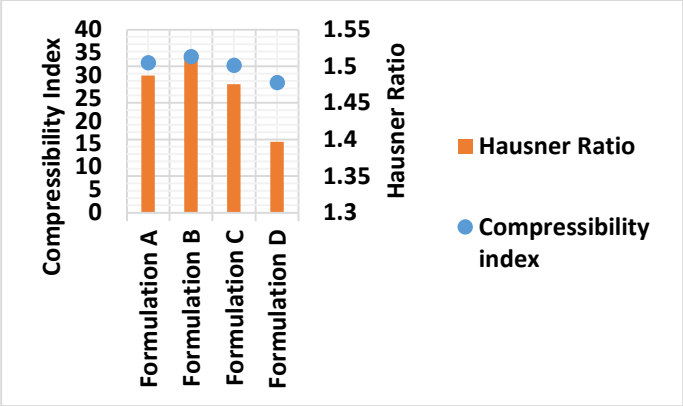

Figure 2a, compressibility index and Hausner ratio

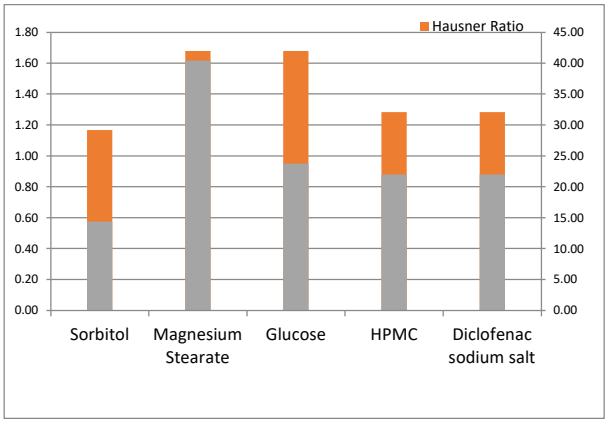

Figure 2b, compressibility index and Hausner ratio (excipient)

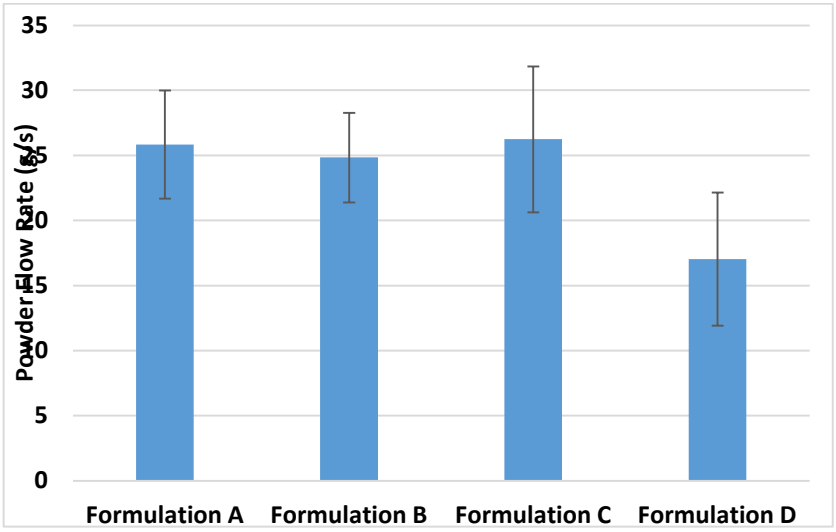

Figure 2c, powder flow

3.3 Friability

The results of friability testing of the uncoated diclofenac sodium buccal tablets for all the formulations A, B, C and D in figure 5, failed the test according to the British Pharmacopeia, friability specification of less 1.0% weight loss. According to report by Osei and Sun, (2015), the friability test is used in guiding formulation development to determine the function of compaction pressure, from which the minimum compaction of force required to identify how strong the tablet is. The test is specifically used to facilitate tablet product development. The friability test is carried out to enhance other physical strength measurements like tablet tensile strength, crushing strength and identification of hardness to determine whether the tablet will pass or fail the acceptance condition. Therefore, tablet friability is very important, and it's more a more reliable test because it provides useful information about the structure-property-performance of the tablet during storage and transportation (Thoorens *et al.*, 2014).

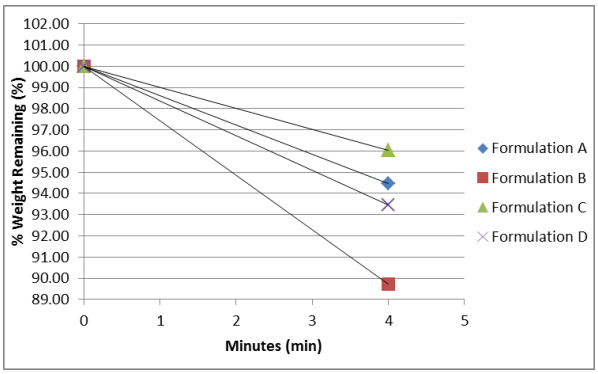

Figure 3, friability test

Conclusion

Buccal drug delivery has attracted more attention from industrial and academic researchers due its advantages and its distinct features that include patient compliance, rapid drug response and avoidance of first path metabolism and to enhance the bioavailability of drug through the buccal mucosa to enhance the release of drug for an extended period. The tablet of all the formulations A to D shows good disintegration and dissolution for a buccal tablet because it does not require disintegrating within fifteen minutes specified by BP and dissolution of all the formulation has a constant release of drugs. The Hausner ratio and compressibility index of all the formulation fall within the range of poor to very, very poor in their respective scales, this indicates that the formulations do not flow in the powder flow testing properly. These may be due the pressure exerted during tablet compaction to give a hard tablet to achieve a unidirectional release of the tablet or due to sorbitol which also give a hard tablet. Therefore, more study should be conducted to evaluate the in vivo drug delivery for this formulation and the powders need to be subjected to granulation processing to produce particles with pre-determined properties.

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