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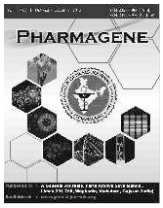

"Biodegradable Chewing Gum Formulation Of Diclofenac Sodium"

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Abstract:

Diclofenac sodium belongs to BCS class-2 drug having poor bioavailability (40-50%) because of first pass effect. The present project aims at increasing bioavailability by administration by buccal route. Chewing gum was prepared as patient compliant formulation for this purpose. Conventional chewing gum base was replaced with a combination of polyethylene oxide and beeswax to increase its biodegradation potential. The prepared chewing gum formulation released above 90% drug within 30 min. and degraded in 7-10 days as compared to 5 years degradation time needed for conventional chewing gum.

Key Words :

Introduction :

Diclofenac sodium is approved for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, ankylosing spondylitis. It belongs to BCS class-2 drug having poor bioavailability (40-50%).[1] Despite of being 100% absorbed after oral administration, only 50% of the dose remains systemically active[2] because of hepatic first pass metabolism. Buccal delivery may improve the bioavailability as buccal mucosa is highly vascularized as compared to gastrointestinal tract (GIT).[3,4] This may reduce the dose and also GI side effects are less. An additional advantage of buccal delivery is that termination of therapy is possible in case of acute toxicity or hyper-allergic reactions.

Chewing gum is one of the dosage form that can be used for drug delivery in the buccal cavity. Chewing gums provide patient compliance and thus have been used worldwide since ancient times after man experienced the pleasure of chewing a variety of substance. It can be used as a convenient modified release drug delivery system. Chewing gums have been used for centuries to clean the mouth and freshen the breath.[5-7] The first commercial chewing gum "State of Maine pure spruce gum" was first marketed in the U.S.A and the first patent was filed in 1869. The gum was intended as dentifrices but it has never been marketed. The first Medicated chewing gum was launched in 1928. This chewing gum is still available, contains acetylsalicylic acid.[8-10]

Medicated Chewing Gum (MCG) is a drug delivery system containing masticatory gum base with pharmacologically active ingredient and intended to use for local treatment of mouth diseases or systemic absorption through oral mucosa. Chewing gum is a mixture of natural or synthetic gums and resins sweetened with sugar, corn syrup, artificial sweeteners and may also contain colouring agents and flavour. The basic raw material for all CG is natural gum Chicle, obtained from the sapodilla tree. Chicle is very expensive and difficult to procure therefore other natural gum or synthetic materials like polyvinyl acetate and similar polymers can be used as gum base. Most of the elastomers used for chewing gums, though natural in origin do not degrade easily, and hence are the cause of soil pollution. Average time of degradation of chewing gums in soil is approx. 5 yrs.[11] Use of biodegradable polymers as chewing base will reduce the environmental pollution caused by conventional chewing gum.

Therefore, in the present research work biodegradable chewing gums were developed as a patient compliant formulation for buccal delivery of diclofenac sodium. This chewing gum is expected to increase the bioavailability of diclofenac sodium in a pleasant manner and without having deleterious effect on environment.

MATERIALS AND METHODS

Diclofenac sodium was a gift sample provided from Centurion Laboratories, Vadodara. Poly ethylene oxide, beeswax and dextrose were procured from Qualikems fine chem. Pvt. Ltd., Vadodara. Calcium carbonate and talc were purchased from Sulab Laboratories, Vadodara.

METHODS

Preparation of Chewing Gum

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Various batches of chewing gums were prepared by direct compression technique (Table 1). Briefly, all the ingredients were blended in geometrical ratio in mortar with a pestle for 15 minutes to obtain uniform mixture. The blended powder was then compressed (3-4 kg/cm^2) by rotary tablet machine. Compostion of chewing gum include polymers, plasticizer, filler (calcium carbonate), sweetener (dextrose), flavor (peppermint oil), lubricant (magnesium stearate) and glidant (talc).

Plasticizer screening was done on the basis of drug release profile. Glycerol and castor oil were tested for this purpose.

Optimization Study

The concentration of biodegradable polymer (Polyethylene oxide) (X1) and concentration of plasticizer (Glycerol) (X2) were chosen as independent variables, while In-vitro drug release study (Y) was taken as dependent variable. Total nine batches (Table 2) were prepared according to 3^2 full factorial design.

Powder blend analysis

The blend evaluation was performed for flow property and compression characteristics.

Angle of repose

Powder blend were allowed to flow through the funnel freely onto the surface. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the powder. The diameter of the powder cone was measured. It was measured by following formula:

$$\tan\theta = h/r \qquad \text{Where , h=height; r=radius}$$

Derived Properties of Powder Blend

First the bulk and tapped densities of the powders were measured. Carr's index and Hausner's ratio of the powder blend was calculated by using the following formulas

$$\%\ \text{compressibility} = \frac{\text{Tapped density - Bulk density}}{\text{Tapped density}} \times 100$$

$$\text{Hausner's ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Bulk density

Volume of 10 g powder blend was measured using measuring cylinder. The volume was adjusted by small tap to obtain flat volume and measuring the volume occupied by powder.

$$\text{Bulk density} = \frac{\text{Mass of blend (gm)}}{\text{Bulk volume (ml)}}$$

Tapped density

Tapped density has been measured using tap density apparatus by measuring the volume occupied by powder after 100 taps for 20 min.

$$\text{Tapped density} = \frac{\text{Mass of blend (gm)}}{\text{Tapped volume (ml)}}$$

Hardness

This study was performed as done for tablets12 using Pfizer hardness tester. The pressure required to break the tablet was determined by visual reading on Pfizer hardness tester.

Friability

Friability of the tablet was performed as discussed using Roche friability testing apparatus.13 This device subjects the tablet to the combined effect of abration and shock in plastic chamber revolving at 25 rpm. Preweighed samples were placed in the friabilator and subjected to the 100 revolutions. Tablets were de-dusted using a soft muslin cloth and reweighed. The friability (F) is given by the formula.

$$F = \frac{W_{initial} - W_{final}}{W_{initial}} \times 100$$

Weight variation test

This test was performed according to Indian Pharmacopoeia.[14] Briefly. 20 tablets were weighed individually and average weight was calculated and maximum % deviation was found. The tablets meet the IP test if not more than two tablets are outside the % limit and if no tablets differs by more than two times.

Drug content

The drug content was performed as discussed in Indian Pharmacopoeia 2007[15]. Briefly, 20 tablets were weighed and grounded in a mortar with pestle to get fine powder; powder equivalent to the mass of the one tablet was dissolved in methanol and filtered through Whatmann filter paper. The drug content was analyzed by UV spectrophotometer at 285 nm after suitable dilutions with methanol.

In-vitro drug release study

In vitro dissolution study was performed according to the method reported by Mehta et al (2010), Margrethe et al (1994), Shizard et al (2007)[16-18] using modified chewing gum apparatus. The chewing gum was inserted between the pistons on to the lower chewing surface. The chewing procedure consisted of up and down stroke of lower masticating surface combined with movement of upper masticating surface, thereby masticating the chewing gum and consequently agitating the test medium. At predominant time interval aliquot of the simulated salivary fluid, were removed and assayed for drug content by UV spectrophotometric analysis. Same volume of the release medium was replaced with fresh artificial saliva after each sample was taken to maintain the sink condition.

Dissolution parameters

Dissolution Apparatus	Modified chewing gum apparatus
Dissolution media	Simulated salivary fluid pH 6.8
Volume	40 ml
Strokes per min	60 strokes/min
Temperature	37 ± 0.5^0C
Sample volume	5 ml

Biodegradation Study

Biodegradation study was performed as discussed by Ratajska M et al (2003).[19] Firstly, an active sludge from the waste water was taken and used as the source of microorganism, filter the water using normal filter paper. Then this water used as an

aqueous medium for the biodegradation process. Then the powder blend of optimized batch (F10) was taken in the petri dish and added above filtered waste water in to it. Then the petri dish containing the powder blend with waste water kept at room temperature and evaluate for weight loss by physical examination (visually).

RESULT AND DISCUSSION

Screening of plasticizer

Glycerol, when used as plasticizer showed faster release (Table 2) as compared to castor oil. Also, formulations containing castor oil resulted into soft and discoloured finished product. Also, castor oil may be prone to oxidation, a demerit with oils. Therefore, glycerol was selected as plasticizer for further studies.

Table 1: Screening of plasticizer

	Glycerol				Castor oil			
Batch no.	P1	P2	P3	P4	P5	P6	P7	P8
Diclofenac sodium (mg)	75	75	75	75	75	75	75	75
Poly ethylene oxide (mg)	400	400	400	400	400	400	400	400
Plasticizer* (mg)	40	50	60	70	40	50	60	70
Bees wax (mg)	60	60	60	60	60	60	60	60
Dextrose (mg)	50	50	50	50	50	50	50	50
Peppermint oil (mg)	10	10	10	10	10	10	10	10
Talc (mg)	1	1	1	1	1	1	1	1
Mg. stearate (mg)	1	1	1	1	1	1	1	1
Calcium carbonate (mg)	qs*	qs*	qs*	qs*	qs*	qs*	qs*	qs*
T50% (min.)	25	25	20	15	40	35	35	30

* Tablet weight 700 mg

Optimization studies

Release of drug from biodegradable chewing gum of diclofenac sodium varies according to the concentration of biodegradable polymer (Poly ethylene oxide) and glycerol. In almost all the formulation, In-vitro drug release data close to the expected desired range of 90% to 99% in 30 min.

The in-vitro drug release profile of batch F1 to F3 were ranging between 44.12±0.01 to 50.69±0.01 within 10 minutes. Also at the end of 30 minutes, the cumulative percent drug release was found to vary from 92.47±0.11 to 95.3±0.12. On physical examination of biodegradable chewing gum during dissolution study, it was found that after amount of drug released completely from dosage form, only the some amount of polymer and other excipients were remaining, which was discarded.

The in-vitro drug release profile of batch F4 to F6 were ranging between 41.11±0.16 to 52±0.09 within 10 minutes. Also at the end of 30 minutes, the cumulative percent drug release was found to vary from 96.24±0.17 to 99.41±0.20. The in-vitro drug release profile of batch F7 to F9 were ranging between 31.32±0.16 to 51.47±0.10 within 10 minutes. Also at the end of 30 minutes, the cumulative percent drug release was found to vary from 90.84±0.15 to 95.64±0.14.

Table 2: Optimization of diclofenac chewing gum formulation by 3^2 factorial design

Batch	Coded values		Real values		DR in 30 min.
	X1	X2	Poly ethylene oxide (mg)	Glycerol (mg)	%
F1	-1	-1	350	55	95.3±0.115
F2	-1	0	350	60	94.89±0.139
F3	-1	1	350	65	92.47±0.108
F4	0	-1	400	55	96.24±0.166
F5	0	0	400	60	99.41±0.204
F6	0	+1	400	65	97.33±0.165
F7	+1	-1	450	55	90.84±0.151
F8	+1	0	450	60	95.64±0.143
F9	+1	+1	450	65	93.90±0.293

A quadratic model, having significant p-value (0.0274) was suggested by DX7 software. The p-value for linear factors were found to be >0.05, therefore those two terms were removed from the equation. The reduced equation resulted into:

$$\% \text{ Drug release} = 99.19 + 1.47 * A * B - 3.82 * A^2 - 2.30 * B^2$$

The optimized formula was derived to be formulation containing 400 mg PEG and 60 mg glycerol. The relationship between variables was further elucidated using contour plot. The effects of X1 and X2 is given in the figure

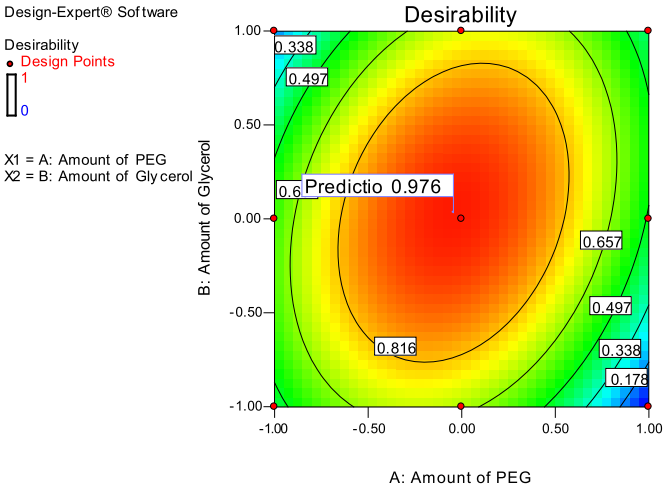

Figure 1: Contour plot In-vitro drug release for F1 to F9

Biodegradation study:

Biodegradation study was carried out by using waste water which contains the microorganism; participating in biodegradation process provided the natural environment for the biodegradation. The prepared chewing gum showed biodegradation within 7-10 days.

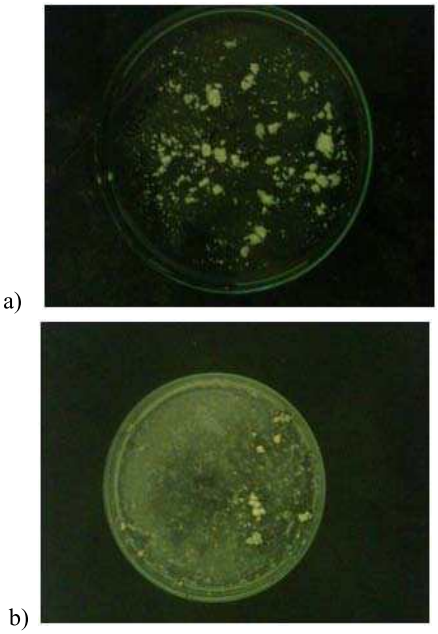

Figure 2: Biodegradation result after incubating in waste water on a) Day 1, b) Day 7

CONCLUSION

A biodegradable chewing gum formulation was developed to improve the bioavailability of diclofenac sodium. The prepared formulation can release the drug within 30 min. and it is not expected to cause soil pollution as biodegradation occurs within 7-10 days.

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