Design and evaluation of mucoadhesive buccal Tablets of Isosorbide dinitrate

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Abstract

The present investigation is concerned with formulation of buccoadhesive tablets of Isosorbide dinitrate to circumvent the first pass effect and to improve its oral bioavailability with reduction in dosing frequency. Tablets of Isosorbide dinitrate Were prepared by direct compression method using different combinations of bioadhesive polymers like sodium CMC , sodium alginate, HPMC, Carbapol-934.mannitol is incorporated in different concentrations .The physical characteristics such as Swelling index, Surface PH, *invitro* bioadhesion $t_{1/2}$ is strength, *invitro* release of formulated tablets were found to be dependent on Characteristics and composition of bioadhessive materials used. the bioadhesion strength of selected ratios (1:1) were F13>F1>F9>F5.The *invitro* profile from selected ratios (1:1) are in order of F5>F9>F1>F13.All the formulations showed stability for the span of six months at the room temperature.

Introduction

Buccal delivery of drugs provides an attractive alternate to the oral route of drug administration, particularly in over coming deficiency associated with the latter mode of dosing. Substantial efforts have recently been focused upon placing a drug or drug delivery system in a particular region of the body for extended period of time .This need is not only the local targeting of drugs but also for a better control of systemic drug delivery (1) .mucoadhesive drug delivery systems are delivery systems, which utilize the property of bioadhesion of certain polymers, which become adhesive on hydration and hence can be used for targeting of drug to particular region of the body (2)

Isosorbide dinitrate is a long acting nitrate used as an antianginal in myocardial infection. The main drawback of conventional Isosorbide dinitrate formulation is that it undergoes hepatic first pass metabolism by enzymatic denitration. Thus the plasma t1/2 is 45-60 min thereby decreasing its bioavailability . The conventional sublingual tablets (5-10mg) produce maximal concentration is rapid. Hence an alternative delivery system for improving the onset of action and needed.(3)

In the present investigation attempts have been made to design efficacious and prolonged release buccoadhesive tablets of Isosorbide dinitrate using various bioadhesive polymers to avoid first pass metabolism, to reduce dosing frequency and to improve patient compliances

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Materials and methods

Isosorbide dinitrate is obtained as gift samples from Bangalore Pharmaceutical Research Lab,Bangalore.Carbapol 934 from geneuine chemicals co Mumbai,SCMC from Ranbaxy Laboratory ltd.Delhi HPMC and Sodium alginate from ontop-pharmaceuticals Bangalore.

Methods

Preparation of buccoadhesive tablets of Isosorbide dinitrate were prepared by direct compression method .All the ingredients except magnesium sterate were passed through # 100 and were blended in glass mortar uniformaly after the sufficient mixing of drug as well as other components .the magnesium sterate was added and mixed for additional 2 to 3 min .The tablets were compressed using 6mm flat faced tablet punches at pressure of 300kgs/sq cms.

In this study 16 formulations (F1 to F16) of buccoadhesive tablets of Isosorbide dinitrate in concentration of four different bioadhesive polymers in drug at ratios [1:1,1:2,1:3,1:4] [Table no I]

Evaluation of buccoadhesive tablets:

Physicochemical properties: All the formulations of buccoadhesive tablets were evaluated for uniformity of weight (4),drug content(5) ,friability (6),hardness(7) ,tensile strength (8),swelling studies (9) and surface PH(10) invitro- bioadhession (11,12) Bioadhesion strength of the tablets were measured using modified physical balance(13) .all the equipments were conducted in triplicate.

In-vitro drug release studies (14,15) The donor tube attached with buccal tablets was introduced into the

receptor compartment containing 150ml of pre warmed (37±1)phosphate buffer PH 6.8 in such a way that tablet releasing surface remained at 0.5 inch above the bottom of beaker. The temperature was maintained at 37±1 with an energy controlled hot plate with a magnetic stirrer .Dissolution fluid was stirred at a constant speed at 50 rpm using Teflon coated iron bead. Aliquots (10ml) were withdrawn and filtered through whatmann filter paper no 42.The same volume of pre warmed phosphate buffer was introduced into the receptor compartment after each withdrawal, all test and blank samples were assayed spectophotometrycally at wave length 220nm.

Stability study : The optimized formulations (F1, F5, F9, F13.) were Subjected to stability testing at 40 ±1 and75±1 in two different temperature adjusted in hot air oven. The tablets were removed from oven at the end of every 24 hours for seven days; analysed drug content and average of triplicate reading were taken.

Result and discussion

The main objective of this work was to enhance therapeutics performance of Isosorbide dinitrate by developing buccoadhesive tablets .carbapol 934, SCMC, HPMC and sodium alginate were selected as buccoadhesive polymers.

All the formulations showed acceptability results with respect to weight variation, drug content, and friability. The weight variation and hardness of tablets were found to be with in the official limit. The hardness is between 4.83 to 5.33 kg/sq cms the slight variation of hardness were due to variation in the official limits. All the formulations showed less than 1% friability that indicates ability of tablets to withstand shocks which may be uncounted during transportation, no significant difference was observed in the thickness of individual tablet from the average thickness

Invitro swelling study: swelling index was calculated with respect to time (Table no.2).The swelling values of tablets containing carbopol 934 and sodium alginate is more as compared to other formulations. It was observed that when tablet come in contact with aqueous medium, wetting occurred first at the lower surface and then progressed to whole. After Surface PH determination tablets of all batches showed a surface PH in the Range of 5-7 that indicates no risk of mucosal damage or irritation.

In vitro bioadhesion characteristics were found to be affected by the type and ratio of bioadhesive polymer .The highest bond strength was possessed by F13 i.e with carbapol-934 and the order of bioadhesive of some selected formulations (1:1) were F13>F1>F9>F5

Invitro release was carried out and the release profile from selected formulations (1:1) were in the order of F5>F9>F1>F13 it shows the release is in the range of 83 to 98 % for the extended period of 5 to 7 hrs. The Release with HPMC polymer is 98%, sodium alginate 94% and SCM 88%,Carbapol-934 83% respectively. Stability study, the buccoadhesive tablets were found stable at room temp with respect to drug content.

Table No.1

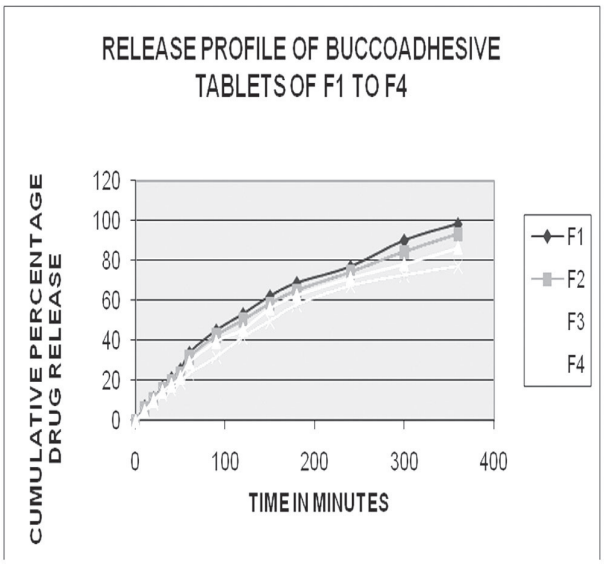
FORMULAE OF DIFFERENT BUCCOADHESIVE TABLETS OF ISOSORBIDE DINITRATE

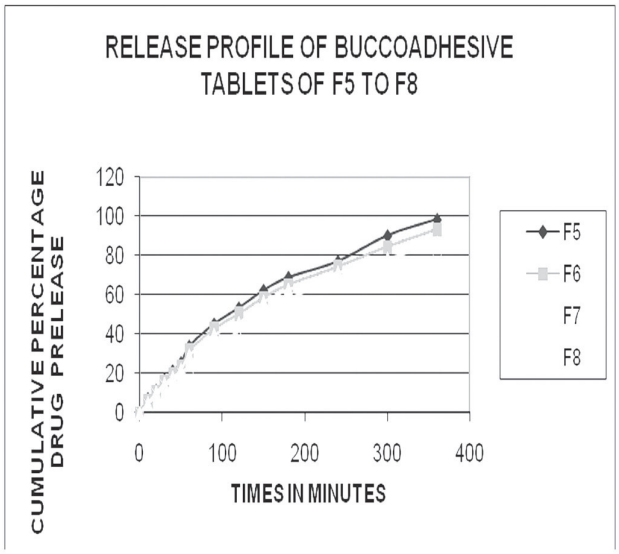
SL.NO	Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1	Isosorbide dinitrate	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
2	Sodium carboxy methyl cellulose	10	20	30	40	-	-	-	-	-	-	-	-	-	-	-	-
3	Hydroxyl propyl methyl cellulose	-	-	-	-	10	20	30	40	-	-	-	-	-	-	-	-
4	Sodium alginate	-	-	-	-	-	-	-	-	10	20	30	40	-	-	-	-
5	Carbapol-934	-	-	-	-	-	-	-	-	-	-	-	-	10	20	30	40
6	Mannitol	75	65	55	45	75	65	55	45	75	65	55	45	75	65	55	45
7	Magnesium stearate	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2	2
8	Talc	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3

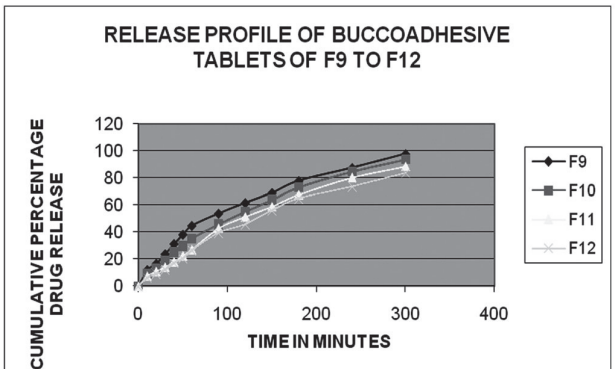
Table No. 2
PHYSICAL CHARACTERISTICS OF PREPARED BUCCOADHESIVE TABLETS

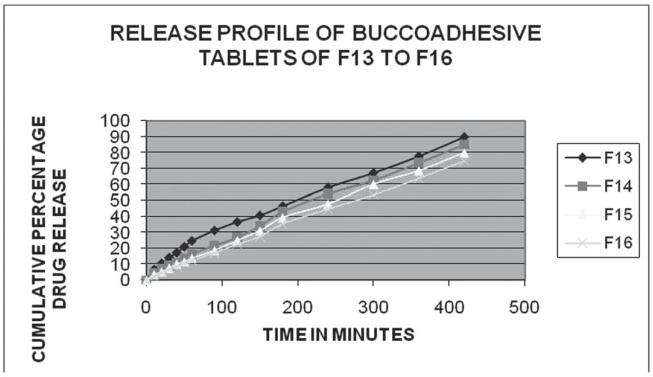
Formulation	Hardness* in kg/ sq.cm.	Friability* in %	Thickness* in mm	Bioadhesion strength in gm	Drug content in %	Weight variation* in mgs	Swelling index * in hours
F1	4.83	0.31	1.96	13.8	101.2	101.1	63.53
F2	4.96	0.30	1.96	15.8	96.05	100.9	66.57
F3	4.90	0.24	2.03	18.6	94.25	100.1	58.51
F4	4.86	0.21	2.10	20.3	92.60	100.5	68.20
F5	5.20	0.42	2.06	08.4	99.90	101.5	47.52
F6	5.03	0.41	2.06	10.6	93.50	99.60	38.12
F7	5.03	0.38	2.00	13.8	92.50	101.9	43.13
F8	5.16	0.29	2.13	15.4	90.10	99.70	49.74
F9	4.93	0.62	2.13	11.3	98.80	99.50	72.03
F10	5.23	0.61	2.10	12.5	96.20	100.3	78.31
F11	5.20	0.57	2.06	15.5	94.60	99.90	82.63
F12	5.23	0.51	2.00	17.4	92.80	100.8	89.00
F13	5.16	0.72	2.10	15.5	95.94	101.0	103.5
F14	5.12	0.74	2.16	18.6	91.50	101.6	106.0
F15	4.86	0.63	2.03	22.8	90.52	101.8	123.0
F16	5.33	0.59	2.06	25.7	90.52	101.1	168.5

*** Values are represented as mean , n=3**









CONCLUSION

It can be concluded that stable formulations of the investigations were encouraging. Hence there is a scope to study the influence of co-polymers on release profile .and the in vivo evaluation of buccoadhesive tablets using various animal models.

ACKNOWLEDGEMENTS

I am thankful to Dr. I.S.Muchandi, Principal, HSK College of Pharmacy Bagalkot, for providing me the basic facilities to carry out my research work. I am also thankful to Bangalore pharmaceutical research lab,Bangalore for providing the gift sample.

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