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Formulation and Evaluation of Metformin Hydrochloride Buccal Patch

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ABSTRACT
Transdermal drug delivery system is a self-contained delivery system used for topical application in the form of a multilaminated adhesive patch, which delivers a specific dose of drug at a predetermined rate and controls the drug release rate through the skin. This system provides constant drug release and enables continuous delivery of drugs with short biological half-lives, eliminating pulsed entry into the bloodstream. Several drugs that would otherwise degrade in the gastrointestinal tract have been successfully administered via this route. This method is especially beneficial for patients experiencing repeated emesis or dysphagia, who are unable to swallow large amounts of water. In this context, the significance of oral transmucosal drug delivery and its advantages over conventional oral delivery systems has been emphasized. Chronic hyperglycemia, as seen in diabetes, leads to long-term damage and dysfunction of organs, necessitating long-term medication. Metformin, an antihyperglycemic agent for type 2 diabetes, has poor bioavailability (50–60%) and a short biological half-life, requiring frequent high-dose administration. Glibenclamide, another oral hypoglycemic agent, is commonly used as well. This study aims to develop a polymer-based (chitosan) oral disintegrating film system for metformin, overcoming its limitations through improved delivery and bioavailability. The disintegration and bioavailability of these oral thin films (OTFs) are enhanced using super-disintegrants like starch, sodium starch glycolate, and microcrystalline cellulose. This approach offers a rapid, efficient drug delivery method. As diabetes prevalence is expected to rise significantly by 2025, such innovative delivery systems could provide a practical solution for improving therapeutic outcomes.

I. INTRODUCTION

Transdermal drug delivery system is a self-contained delivery use for topical application in the form of multilaminated adhesive patch which gives a specific dose of drug at a predetermined rate and controlled the rate of drug release through skin.[1]

This delivery provides the constant drug release but it also allows the short biological half life drug continuously and eliminates the pulsed entry into the blood circulation [2] .

Several drugs that would otherwise undergo degradation in the gastrointestinal tract have been successfully administered by this route.[3]

This suits patients suffering from repeated emesis, dysphagia, etc, who cannot swallow a large quantity of water. In this context, several research groups have highlighted the importance of oral transmucosal drug delivery and its future prospects over conventional oral drug-delivery systems[4]

The chronic hyperglycemia is associated with long-term damage, dysfunction and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels. Thus diabetes covers wide ranges of heterogeneous disease. Several groups of drugs, mostly given by mouth are effective in type2 diabetes mellitus.3 Metformin is Antihyperglycemic agent which improves glucose tolerances in patients with type 2 diabetes mellitus. Its pharmacologic mechanism of action is different from other classes of oral Antihyperglycemic agents. The absolute bioavailability of a metformin HCl under fasting condition is approximately 50 to 60 %.gastrointestinal absorption occurs mainly in the upper intestine and is completed at 6 hours, with peak plasma concentration [Cmax] reached after 2to3hours.the drawback being high dose [1.5-2g/day] low bioavailability [40-60%], short biological half-life [0.9-2.6hrs] requires repeated administration of high doses to maintain effective plasma concentration.4, 5, 6 Glibenclamide is an

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oral hypoglycemic agent belonging to the second generation of sulfonylurea's used in treatment of type2 non-insulin dependent diabetes.[5]

Therefore, the purpose of the study reported here was to develop a polymer (chitosan)-based oral disintegrating systems of metformin in the form of thin films. Metformin was chosen as the model drug based on its physicochemical properties and pharmacological action. The main limitations of metformin toward therapeutic effectiveness – its poor bioavailability (50%–60%), short biological half-life (5 hours), having the proximal small intestine as its main site of absorption, and the maintenance of adequate plasma levels of the drug are overcome by this method of systemic drug delivery quite satisfactorily.[6]

The bioavailability and disintegration properties of OTFs in saliva are increased by adding different ratios of super-disintegrants such as starch, sodium starch glycolate (SSG), and microcrystalline cellulose (MCC). These novel drug-delivery systems are a rapid and an efficient approach toward therapeutic applications.[7]

An estimated 20.8 million. World wide prevalence of diabetes for all groups of ages estimated in 2000 (2.8%) in future 2030 it would be (4.4%) Centers for sickness control and cure predicts that diabetes will go up by the year 2025, (37.5%) [8].

EVALUATION OF BUCCAL PATCHES :-

Thickness[9]

The thickness of patch was measured by screw gauge with least count 0.001 mm. The thickness uniformity was measured at three different sites and average of three readings was taken with standard deviation.

Weight variation[10]

The three dicks of 1 cm^2 was cut and weighed on electronic balance for weight variation test. The test was done to check the uniformity of weight and thus check the batch-to-batch variation.

Moisture uptake[11]

The percent moisture absorption test was carried out to check the physical stability and integrity of the patches at high humid conditions. In the present study the moisture absorption capacities of the patch were determined in the following manner. The patches were placed in the dessicator containing saturated solution of aluminum chloride, keeping the humidity inside the dessicator at 79.5% R. H. After 24 hrs. The patches were taken and weighed the percentage moisture absorption of the patches was found.

Water vapor transmission test [12]

Vapor transmission method was employed for the determination of vapor transmission from the patch. Glass –bottle (length= 5 cm, narrow mouth with internal diameter = 0.8 cm) filled with 2 gm anhydrous calcium chloride and an adhesive (Feviquick®) spread across its rim, was used in the study. The patch was fixed over the adhesive and the assembly was placed in a constant humidity chamber, prepared using saturated solution of ammonium chloride and maintained at 37±2°c. the difference in weigh after 24 hr. was calculated. Vapor transmission rate was obtained as follows:

VTR = (Amount of moisture transmitted) / (Area × Time)

Tensile Strength [13]

Satisfactory bioadhesion is essential for successful application of biodhesion drug delivery systems in order to increase the residence time at the site of application and hence to provide the prolonged release of the drug. The tensile strength required to detach the bioadhesive patch from the mucosal surface was applied as a measure of the bioadhesive performance. Several techniques have been reported in literature for measurement of bioadhesive strength. In the present work specially fabricated assembly based on published literature of Gupta et. al was used. Goat buccal mucosa was used as the model surface for bioadhesion testing. After the buccal mucosa was excised and trimmed evenly, it was then washed in phosphate buffer and used immediately.

Folding Endurance:[14]

The folding endurance of each patch is determined by repeatedly folding the patch at the same place till it is broken or folded up to 300 times, which is considered satisfactory to reveal good film properties.

Surface pH: [14]

The prepared buccal patches are left to swell for 2 hrs on the surface of an agar plate, prepared by dissolving 2% (w/v) agar in warm phosphate buffer of pH 6.8 under stirring and then pouring the solution into a Petri dish till gelling at room temperature.51 The surface pH is determined by placing pH paper on the surface of the swollen patch. The mean of three readings is recorded.

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Drug content uniformity:[14]

For drug content uniformity, a 3 cm patch (without backing membrane) is separately dissolved in 100 ml of ethanol and simulated saliva solution (pH 6.2) mixture (20:80) for 12 h under occasional shaking. The resultant solution is filtered and the drug content of is estimated spectrophotometrically. The averages of three determinations are taken.

Swelling Index:[14]

Buccal patches are weighed individually (W1) and placed separately in petri dishes containing phosphate buffer pH 6.8. The patches are removed from the petri dishes and excess surface water is removed using filter paper. The patches are reweighed (W2) and swelling index (SI) is calculated as follows: SI = (W2-W1)/W1excess surface water is removed using filter paper. The patches are reweighed (W2) and swelling index (SI) is calculated as follows: SI = (W2-W1)/W1

Moisture Content and moisture absorption :[14]

The buccal patches are weighed accurately and kept in dessicator containing anhydrous calcium chloride. After 3 days, the patches are taken out and weighed. The moisture content (%) is determined by calculating moisture loss (%) using the formula:

Moisture content (%) = Initial weight - Final weightx100/Final weight

Viscosity[15]

Viscosity of Manilkara zapota seed gum was determined using Brookfield viscometer.1 %(w/v) solution of gum.

Preparation and evaluation of metformin hydrochloride sustainedrelease tablets[16]

The studies were carried to find the effect of different concentrations ranges of polymers. Evaluation data of metformin hydrochloride sustained-release tablets were shown in Table 1. All the tablets were having beveled edged flat surface in round shape with white color. Average weight of tablets was in the range of 740–769 mg and weight variation was according to the limits. Thickness of the tablets was in the range of 4.18–5.32 mm. The hardness of tablets was determined and found in the range of 6.10–7.41 Kg/cm2 . As the aim of the study is to release the drug slowly, hardness was kept in the high range. The % of content uniformity in tablets was determined by UV spectrophotometer (Shimadzu, Japan). All formulations are subjected to content uniformity and were in the range of 98.4–101%. It was observed that all the formulations were as per I.P. specification limits (90.0–110.0%). The % drug release data and plot which were obtained for the metformin hydrochloride sustained-release tablets in 0.1N Hcl in first 2 h and phosphate buffer pH 7.4 up to 12 h at 233 nm was shown in Table 2. and Fig. 1. respectively. From the drug release it was observed that at low concentrations of the polymers, the matrices of the tablets readily disintegrated during dissolution test. This was not, however, the case when the content of the matrix former was increased, thus indicating that a minimum level of the polymers is required to form a proper matrix that would not readily disintegrate. This study revealed that as the concentration of matrix material increased, drug release from matrices decreased. This may be due to slower penetration of the dissolution medium into the matrices. Formulations with chitosan drug release were 86% for MS1, xanthan gum was 89% for MS4, and finally MS7with hydroxypropyl methyl cellulose for 92% which exhibited highest drug release retardation with the lowest matrix concentration. Hence, a lower concentration of polymers is suitable to prepare metformin hydrochloride tablets compared to higher concentrations. The initial drug release may be attributed to “burst” release of the drug on the tablet surface. It has stated that the drug particles present on the surface of a matrix systemwere initially released into the surrounding media generating many pores and cracks which facilitate further release of drug and also the formation of channels within the matrix. To describe the kinetics of drug release from matrix tablets, release data were analyzed according to different kinetic equations. The data were analyzed by the regression coefficient method and regression coefficient values (r2) of all batches. On analyzing regression coefficient values of all batches, it was found that tablets exhibited almost zero-order kinetics, followed Higuchi model. The in vitro release profiles of the drug from all these formulations could be best expressed by Higuchi’s

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equation as the plots showed the highest linearity (r2 =0.98–0.99). To confirm diffusion mechanism, the data were fitted into Korsmeyer-Peppas equation.

Formulations with chitosan MS1 drug release are 86%, xanthan gum MS4 was 89%, and finally MS 7 with hydroxypropyl methylcellulose was 92% which exhibited the highest drug release retardation, also had the lowest matrix concentration. Hence, a lower concentration of polymer such as hydroxypropyl methylcellulose is optimized batch suitable to prepare metformin hydrochloride tablets compared to higher concentrations. On analyzing regression coefficient values of all batches, it was found that tablets exhibited almost zero-order kinetics, followed Higuchi model.

Table:- 01 Evaluation data of metformin hydrochloride sustained-release tablets

Batch No	Weight variation (mg) [a]	Thickness (mm) [b]	Hardness (Kg/cm^2) [b]	Friability (%) °	Content uniformity (%) °
MS1	757±0.86	4.40±0.01	6.10±0.23	0.192±0.57	98.4±0.73
MS2	741±1.16	4.59±0.05	6.85±0.25	0.198±0.12	101±1.61
MS3	762±3.57	4.38±0.88	7.41±0.05	0.218±0.17	99.2±0.12
MS4	759±0.88	4.38±0.07	7.22±0.15	0.236±0.27	99.1±0.40
MS5	758±0.88	4.18±0.07	6.15±0.98	0.216±0.07	99.8±0.19
MS6	769±0.12	5.32±0.07	6.15±0.83	0.226±0.21	99.1±0.14
MS7	740±0.88	4.18±0.03	6.15±0.75	0.246±0.78	99.8±0.78
MS8	743±1.11	4.38±1.12	6.35±0.14	0.219±0.45	99.6±0.69
MS9	745±0.12	4.36±0.15	6.15±0.56	0.286±0.32	99.8±0.42

Table:- 02 % drug release data of metformin hydrochloride sustained-release tablets

Time (H)	MS1	MS2	MS3	MS4	MS5	MS6	MS7	MS8	MS9
0	0	0	0	0	0	0	0	0	0
1	14	17	19	13	16	14	12	15	11
2	20	21	27	22	19	26	22	25	16
3	26	27	30	31	24	32	33	30	22
4	34	33	37	38	29	41	39	36	27
5	41	38	45	44	35	48	49	42	32
6	47	43	55	50	42	52	53	59	39
7	55	53	62	54	57	59	59	63	48
8	67	61	67	62	69	61	63	69	58
9	73	67	71	68	72	65	70	71	61
10	81	71	75	78	79	71	78	75	79
11	83	80	82	82	76	79	86	82	83
12	86	82	85	89	83	85	92	89	87

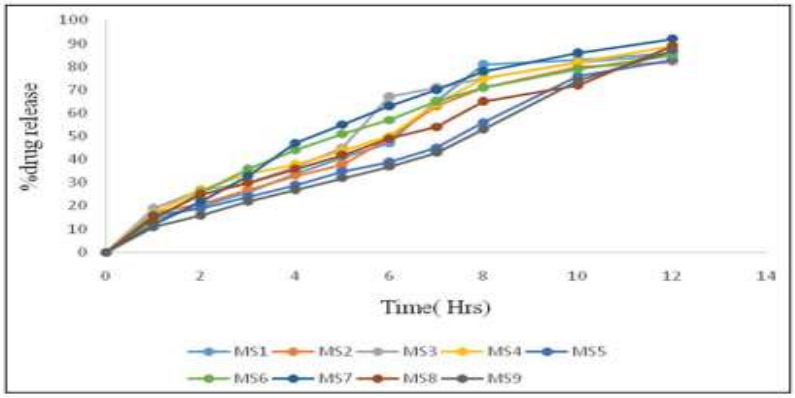

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Fig no:-01 Cumulative % drug release plot of sustained-release tablets

In vitro dissolution studies of the sustained-releaselayer containing metformin hydrochloride[17]

All the formulations subjected to in vitro dissolution studies revealed that tablets containing release modifiers exhibited sustained release of metformin hydrochloride and gliclazide. The dissolution profile of formulations containing metformin hydrochloride was represented in fig. 2 The dissolution profile of metformin hydrochloride formulation revealed that M1-M3 formulations released the drug completely by the end of 12 h, which is probably due to faster dissolution of the highly water-soluble drug from the core and its diffusion out of the matrix forming the pores for the entry of solvent molecules. A suitable sustained-release formulation should release the required amount of drug in the initial hour, followed by slow release. Formulation M4 (30% HPMC K100M) exhibited the slowest dissolution profile which was consistent with USP specification. In contrast, the release of metformin hydrochloride from formulation M5-M7 prepared using polyox WSR coagulant was extended up to 24 h. Batch M7 prepared by direct compression method using polyox WSR coagulant (25%) exhibited a good drug release profile. Data of comparison of formulations M4 and M7 with innovator by similarity and dissimilarity factor represented in table 3 reveals that M7 is the promising batch and selected as the best formulation for further studies.

Table 3. Comparision of formulations with innovator by similarity and dissimilarity factor

Formulation	f2 value	f1 value
M4	72.05	3.6
M7	79.95	2.36

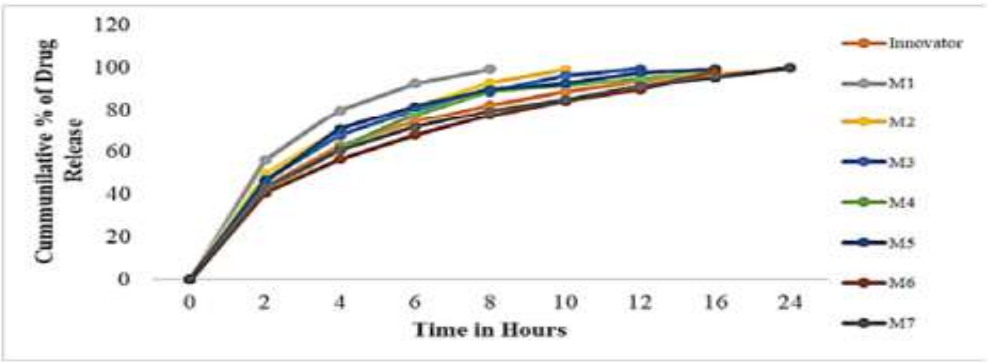

Fig. 2 In vitro dissolution profile of Metformin hydrochloride formulation M1-M7 and innovator

Sustained-release layer containing gliclazide

The dissolution profile of gliclazide formulations was represented in fig. 3. Formulation G3 and G6 displayed a cumulative release of nearly 98.7% and 99.6% in 12 h and 16h respectively where 40% of polymers HPMC K4M and K15M were employed. In contrast, the formulation G8 exhibited a better-controlled release profile of 99.8% at 24 h as represented in fig. 5.

Here, the polymer HPMC K100M showed a better rate of retardant ability than the above two variants at a lesser concentration. The hydration rate of HPMC increases with an increase in the Hydroxyl Propyl content and the solubility of HPMC is pH-independent [18]. The water-repelling property of higher variants of HPMC retarded the drug release from the matrix by preventing the penetration of solvent molecules. HPMC K100M was judiciously selected in preparation due to its profound ability to form a strong viscous gel on contact with aqueous media, which helps in controlling the delivery of highly water-soluble drugs [19].

Final compression of bilayer tablets

Based on results of in vitro dissolution

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studies batch M7 of metformin hydrochloride and batch G8 of gliclazide were selected to prepare bilayer tablets. Initially, the metformin hydrochloride blend was poured into the die cavity and compressed with moderate force. Then the upper punch was lifted and the gliclazide granules were poured in the die cavity, containing initially compressed layer 1 and compressed with full force to form a bilayer tablet of 1000 mg with a hardness of 7-8 Kg/Cm2 using Cadmach single punch compression machine with 12 mm concave punch and die [20].

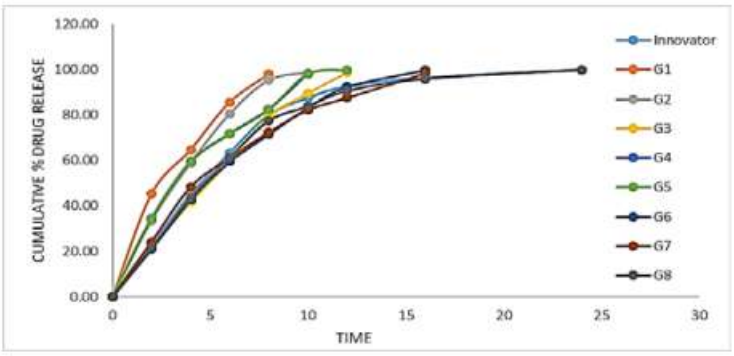

Fig. 3: In vitro dissolution profile of gliclazide formulation G1-G8 and Innovator

The dissolution profiles of the individual layer in the final formulation were compared with the innovator (Exermet GZ 560). From the graphs, it is evident bilayer tablet shows a similar release pattern as Exermet GZ 560 with a good similarity factor 79.95 and 73.62 for metformin hydrochloride and gliclazide respectively. The post-compression parameters of the bilayer tablets were found to be within the limits.[17]

Preparation of matrix tablets by melt granulation[21]

Hot melt granulation technique was used to prepare the drug-wax matrix formulations. First stearic acid was melted in a stainless steel vessel at 75 oC. Metformin HCl was sieved through a 850 µ aperture screen, and heated, spread on a metal tray in an oven at 75 oC. Melt granulation was carried out by transferring the molten metformin HCl to a high shear mixer-granulator (model-Mini RMG, Kevin, India) and then slowly adding the molten stearic acid. Granulation speed was 100 rpm for the impeller and 1500 rpm for the chopper while granulation time was 5 min. The granules were allowed to cool to room temperature by spreading them on metal trays and then sieved through a 850 µ aperture screen. The melt granules were mixed with PEO (presieved through a 850 µ screen) and microcrystalline cellulose (pre-sieved through a 600 µ screen), mixed with colloidal silicon dioxide (pre-sieved through a 425 µ screen) and magnesium stearate (pre-sieved through 425 µ screen). The blend was compressed into 19 x 9.7 mm oblong tablets in an 8- station Cadmach compression machine.

Preparation of matrix tablets by direct compression[21]

Batch M6 was selected for this purpose. The drug and microcrystalline cellulose were sieved through a 850 µ screen and manually blended for 5 min. Colloidal silicon dioxide (pre-sieved through a 425 µ screen) was added next and blended for 3 min. Finally magnesium stearate (pre-sieved through a 425 µ screen) was added and mixed for additional 2 min. The final blend was compressed into 19 x 9.7 mm oblong tablets in an 8-station Cadmach compression machine.

Physicochemical characterization of granules

The granules were evaluated for various physicochemical parameters including angle of repose, bulk density, tap density, compressibility index and Hausner ratio. Angle of repose The fixed-funnel method was used to determine angle of repose. The granule formulation was carefully poured through a funnel until the apex of the conical pile just touched the tip of funnel. The height (h) of the pile of the powder and the radius (r) of its conical base were measured and applied to compute the angle of repose (θ) as in Eq 1 [14]. $\theta = \tan^{-1} h/r$ …… (1)

A 30 g quantity of the granule samples was placed in a 100 ml dry measuring cylinder and volume, Vo, occupied by it, without tapping, was determined. The cylinder was then given 500 taps using a tap density apparatus (model ETD-1020, Electrolab, India,) and the resulting volume, V500,

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was noted determined [15-16]. The bulk and tap densities were calculated using Eqs 2 and 3, respectively.

Bulk density = W/Vo…… (2)

Tapped density = W/V500 ……..… (3)

where W is the weight of the granules

Compressibility index

This parameter was calculated fitting bulk and tap density data (TD and BD, respectively) into Eq 4 [21,22]. Compressibility (C%) = 100 (TD – BD)/TD …. (4)

Hausner ratio This parameter was calculated as the ratio of tap density to bulk density of the granules [21,22].

Physicochemical characterization of tablets

The tablets were evaluated for assay, hardness and friability.

Determination of drug content[21]

Randomly selected tablets (20) from each batch were weighed and powdered. A quantity of the powder, equivalent to 100 mg of metformin HCl, was transferred to a 100 ml volumetric flask and extracted with water. A quantity (1 ml) of filtered solution was diluted to 100 ml with water and the absorbance measured at 233 nm (model UV1201, Shimadzu). Each measurement was carried out in triplicate and the mean taken. Drug concentration was calculated from the calibration curve of a standard (concentration range: 0 to 10 µg/ml).

Determination of tablet hardness[21]

The hardness of each of 10 tablets randomly selected from each batch was measured with a tablet hardness tester, and the mean and standard deviation evaluation.

Determination of tablet friability[21]

Tablet friability was assessed using a friabilator (model EF-2, Electrolab, India) at 25 rpm for 4 min. The weight of ten tablets before and after the test, and the percent loss in weight recorded as friability.

II. CONCLUSION:

The study successfully demonstrates that a chitosan-based oral disintegrating thin film system of metformin can effectively overcome the drug's inherent limitations—such as poor bioavailability, short biological halflife, and high dose requirements—by enhancing dissolution and absorption in the buccal cavity. The incorporation of super-disintegrants like starch, sodium starch glycolate, and microcrystalline cellulose further improves the film's disintegration and drug release profile. This novel drug delivery approach holds promise for improving the therapeutic efficiency of metformin in the management of type 2 diabetes, especially in patients with swallowing difficulties or gastrointestinal intolerance.

REFERENCE

[1]. Jeevanandham S. (2014). Formulation and evaluation of dual transdermal patch containing Metformin hydrochloride - Metoprolol tartarate, International journal of Advanced pharmaceutics, 4(3), 160-164.

[2]. Gaikwad A.K. (2013). Transdermal drug delivery system: Formulation aspects and evaluation- A Reviw. Comprehensive Journal of Pharmaceutical Sciences,1(1), 1 – 10

[3]. Anders R, Merkle HP. Evaluation of laminated mucoadhesive patches for buccal drug delivery. Int J Pharm. 1989;49(3):231–240.

[4]. Sattar M, Sayed OM, Lane ME. Oral transmucosal drug delivery – current status and future prospects. Int J Pharm. 2014;471(1–2):498–506.

[5]. S. Z. Chemate1 , Shruti P. Gosavi ,Formulation Development And In-Vitro Evaluation Of Metformin Hydrocholoride And Glibenclamide Buccal Patch, 2024, Vol 2, Issue 1, 483, file:///C:/Users/A&E/Downloads/document-20240123154637.pdf

[6]. Mura P, Mennini N, Kosalec I, Furlanetto S, Orlandini S, Jug M. Amidated pectin-based wafers for econazole buccal delivery: Formulation optimization and antimicrobial efficacy estimation. Carbohyd Polym. 2015;121:231–240.

[7]. Arya A, Chandra A, Sharma V, Pathak K. Fast dissolving oral films: an innovative drug delivery system and dosage form. International Journal of Chem Tech Research. 2010;2(1):576–583

[8]. Allena RT, Yadav HK, Sandina S, Sarat C, Prasad M. Preparation and evaluation of transdermal patches of metformin hydrochloride using natural polymer for sustained release. Int J Pharm Pharm Sci 2012;3:297-305.

[9]. Agarwal V, Mishra B; Design, development, and biopharmaceutical properties of buccoadhesive compacts of pentazocine; Drug Development and Industrial Pharmacy; 1999; 25(6); 701-709.

[10]. Subhash Deshmane, Madhuri Channawar; Chitosan based sustained release muccoadhesive buccal patches containing Verapamil hudrochloride International journal of pharmacy and pharma science; 2009; 1(s1); 216-230.

[11]. Y Hu, V Topolkaraev, A. Hiltner, E Baer; Measurement of Water Vapour Transmission Rate in Highly Permeable Films; Journal of Applied Polymer Science; 2001; 81(7); 1624-1633.

[12]. Agarwal SS, Munjal P; Permeation studies of Atenolol and MetoprololTartarate form three different polymer matrices for transdermal delivery; Ind Journal of Pharma Sci; 2007; 69(4); 535-539.

[13]. Bottenberg P, Cleymact R, Muynck CD, Remon JP, Coomans D, Michotte Y, Slop D; Development and testing of bioadhesive, fluoride containing slow release tablet for oral use; Journal of Pharmacy and Pharmacology; 1991; 3(7); 457-464.

[14]. Mr Prasad Jumade, DESIGN AND DEVELOPMENT OF MUCOADHESIVE BUCCAL PATCHES, 2019,page no.7,https://shodhgangotri.inflibnet.ac.in/bitstream/20.500.14146/8732/1/synopsis%20-%20mr%20prasad%20jumade.pdf

[15]. Dhruba Sankar Goswami, Manoj Sharmam ,Development Of New Mucoadhesive Polymer From Natural Source, Asian Jourpurnal Of Pharmaceutical And Clinical Research, 2012; Volume 5 suppl 3:247-250.

[16]. PADMAJA BOOKYA, RAMAKRISHNA RAPARLA, HARIKISHAN PRASAD SRIRAMULA, SUNITHA TARRIGOPULA and SRIDHAR VANGA,atal,FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE SUSTAINED-RELEASE ORAL MATRIX TABLETS, Vol 11, Issue 3, 2018,pp 342-345, file:///C:/Users/Rohit/Downloads/admin,+Journal+manager,+70_AJPCR_21211_RA_Query.pdf

[17]. RAJESWARI ALETI, SRINIVASA RAO BARATAM and BANGARUTHALLI JAGIRAPU, FORMULATION AND EVALUATION OF METFORMIN HYDROCHLORIDE AND GLICLAZIDE SUSTAINED RELEASE BILAYER TABLETS: A COMBINATION THERAPY IN MANAGEMENT OF DIABETES,Vol 13, Issue 5, 2021,Page No.343-350, file:///C:/Users/Rohit/Downloads/41339-Article+Text-197417-1-6-20210621%20(3).pdf

[18]. Ediga S. A new simple RP–HPLC method for simultaneous estimation of metformin HCl and gliclazide tablet dosage form. Int J Pharm Biol Sci 2012;2:277-83

[19]. Sudipta D, Arnab S, Himadri SDE. Formulation, in vitro release kinetics and stability interpretation of sustained-release tablets of metformin hydrochloride. Int J Pharm Pharm Sci 2015;7:418-22.

[20]. Santhosh K, Bhagwat P, Prachi U. Bilayer tablet of tramadol and gabapentin for combination pharmacotherapy of neuropathic pain: development and characterization. Int J Appl Pharm 2018;10:100-7.

[21]. Basavaraj K Nanjwade, R Mhase and FV Manvi,atal,Formulation of Extended-Release Metformin Hydrochloride Matrix Tablets,22 June 2011,Page No.375-383,https://www.bioline.org.br/pdf?pr11047