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FORMULATION AND CHARACTERIZATION OF TRANSMUCOSAL DRUG DELIVERY OF LEVOSALBUTAMOL SULPHATE USING MUCOADHESIVE POLYMERS

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ABSTRACT

Delivery of drugs through the buccal mucosa is one of the alternatives to the oral route of drug administration, particularly to those drugs that have high first-pass. Transmucosal delivery is thus a promising area for continued research with the aim of systemic delivery of orally inefficient drugs such as Levosalbutamol sulphate in the treatment of chronic asthma, chronic obstructive pulmonary diseases. Twelve formulations of mucoadhesive tablets were developed with varying concentrations of natural and synthetic polymers. FTIR studies showed no evidence on interactions between drugs, Polymers, and excipients. The variation of hardness was insignificant in batches. Drug release was investigated by using USP Basket method and the results of release rates were analyzed by using correlation coefficient value of Zero order release plot & Higuchi plot. Swelling index of all the formulations were between ranges of 18.56±0.55 to 89.31±0.07. Surface pH, friability, like i*n vitro* residence time and their evaluations like, drug content uniformity are found within the ranges. The *in vitro* study shows drug release from 71.25% to 99.24%, among these the optimized formulation (F8) containing chitosan and Xanthan gum shown highest drug release of 99.24±1.00% at the end of 8 hours which may enhance the absorption of drug with increased residence time in buccal cavity avoiding first pass metabolism also may enhance bioavailability.

KEYWORDS: Levosalbutamol sulphate, Chitosan, Xanthan gum, HPMC, ethyl cellulose, Mucoadhesive drug delivery System.

INTRODUCTION

The cost involved both in terms of money and time in the development of a single new chemical entity has made it mandatory for pharmaceutical companies to reconsider delivery strategies to improve the efficacy of drugs that have already been approved. Among the various transmucosal routes, buccal mucosa has excellent accessibility, an expanse of smooth muscle and relatively immobile mucosa, hence suitable for administration of retentive dosage forms. Our intent, therefore, is to utilize the implication of various approaches for buccal adhesive delivery strategies applied for the systemic delivery of orally less/in efficient drugs, in addition to the widely used local drug delivery.[1, 2]

Drug delivery via the buccal route using bioadhesive dosage forms offers such a novel route of drug administration.[3] Additionally, buccal drug delivery has high patient acceptability compared to other non-oral routes of drug administration.[4] Various advantages and other aspects of this route are elucidated of the following:

1. Ease of administration.
2. Permits localization of the drug in the oral cavity for a prolonged period of time.
3. Offers excellent route for systemic delivery of drugs with high first pass metabolism, thereby offering a greater bioavailability.
4. A significant reduction in dose can be achieved, thereby reducing dose dependent side effects.
5. Drugs which are unstable in acidic environment of the stomach or are destroyed by the enzymatic or alkaline environment of the intestine.
6. The presence of saliva ensures relatively large amount of water for drug dissolution unlike the case of rectal and transdermal routes.
7. It offers passive system for drug absorption and does not require any activation.
8. It can be made unidirectional to ensure only buccal absorption.
9. The buccal mucosa is highly perfused with blood vessels and offers greater permeability than the skin.
10. Termination of therapy is easy.

Types of buccal drug delivery system

1. Buccal patches/films
2. Buccal gels and ointments
3. Buccal tablets

Advances in Buccal Drug Delivery Dosage Forms: Buccal mucoadhesive dosage forms can be categorized into three types based on their geometry (Graph 1).

Type I: It is a single layer device with multidirectional drug release. This type of dosage form suffers from significant drug loss due to swallowing.

Type II: It is a device in which an impermeable backing layer is superimposed on top of the drug loaded bioadhesive layer creating a double-layered device and preventing drug loss from the top surface into the oral cavity.

Type III: It is a unidirectional drug release device, from which drug loss is minimal, since the drug is released only from the side adjacent to the buccal mucosa.[5]

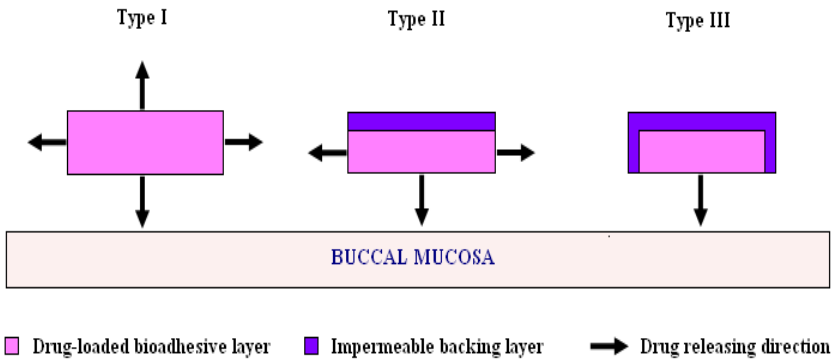


Figure 1: Design of buccal mucoadhesive dosage forms.

Levosalbutamol sulphate is chosen as a drug candidate, which is widely prescribed in the elderly patients as anti asthmatic agent. Levosalbutamol sulphate, (R)-l-{4-hydroxy-3-hydroxymethyl phenyl)-2-(*tert*-butylamino) ethanol sulphate, a β-receptor agonist, is most widely used as a sympathomimetic for the treatment of acute as well as chronic asthma. Generally, it is given through the inhalation route but is also effective after oral administration. But it undergoes first pass metabolism.[6-9]

The anionic and cationic polymers exhibit stronger mucoadhesion. Anionic polymers are the most widely employed mucoadhesive polymers within pharmaceutical formulations. Typical examples include polyacrylic acid (PAA) and its weakly cross-linked derivatives and sodium carboxy methylcellulose (Na CMC).[10, 11] Among the cationic polymer systems, undoubtedly chitosan is the most extensively investigated within the current scientific literature.[12] Chitosan is a cationic polysaccharide, produced by the deacetylation of chitin, the most abundant polysaccharide in the world, next to cellulose.[13] Chitosan is a popular polymer to use due to its biocompatibility, biodegradability and favorable toxicological properties [14]

Chitosan has been reported to bind via ionic interactions between primary amino functional groups and the sialic acid and sulphonic acid substructures of mucus.[15, 16]

Permeation enhancers: The goal of designing penetration enhancers, with improved efficacy and reduced toxicity profile is possible by understanding the relationship between enhancer structure and the effect induced in the membrane and of course, the mechanism of action. Penetration enhancement to the buccal membrane is drug specific.[17]

These permeation enhancers should be safe and non-toxic, pharmacologically and chemically inert, non-irritant, and non-allergenic. The different permeation enhancer's available are.[14-18]

➢ Chelators: EDTA, citric acid, sodium salicylate, methoxy salicylates.

➢ Surfactants: sodium lauryl sulphate, polyoxyethylene, Polyoxyethylene-9-laurylether, Polyoxythylene-20-cetylether, Benzalkonium chloride, 23-lauryl ether, cetylpyridinium chloride, cetyltrimethyl ammonium bromide.

➢ Bile salts: sodium glycocholate, sodium deoxycholate, sodium taurocholate, sodium glycodeoxycholate, sodium taurodeoxycholate.

➢ Fatty acids: oleic acid, capric acid, lauric acid, lauric acid/ propylene glycol, methyloleate, lysophosphatidylcholine, phosphatidylcholine.

➢ Non-surfactants: unsaturated cyclic ureas.

➢ Inclusion complexes: cyclodextrins.

MATERIAL AND METHODS

Levosalbutamol sulphate (**LVS**) was received as Gift Sample by Glenmark Pharmaceuticals Industries Ltd, Nashik. Polymers like Chitosan, PVP K30 and HPMC K4M were obtained from Ozone International, Mumbai. Xanthan Gum and magnesium stearate was received from Meher Chemie, Mumbai and Lactose was received from Thomas Baker, Mumbai. All chemicals used for this study were of analytical reagent grade. Freshly prepared distilled water was used throughout the work.

Levosalbutamol sulphate buccal tablet was prepared by direct compression method.

FORMULATION

Table no.1 Formulation of single mucoadhesive buccal tablet of Levosalbutamol sulphate

Ingredients mg/tablet	Formulation code											
	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12
Levosalbutamol Sulphate	2	2	2	2	2	2	2	2	2	2	2	2
Chitosan	15.60	31.20	46.80	15.60	31.20	46.80	15.60	31.20	46.80	15.60	31.20	46.80
HPMC K4M	--	--	--	15.60	15.60	15.60	--	--	--	--	--	--
Xanthan Gum	--	--	--	--	--	--	15.60	15.60	15.60	--	--	--
Ethyl Cellulose	--	--	--	--	--	--	--	--	--	15.6	15.6	15.6
PVP K-30	4.88	4.88	4.88	4.88	4.88	4.88	4.88	4.88	4.88	4.88	4.88	4.88
Lactose	34.13	24.38	14.63	24.38	14.63	5.85	24.38	14.63	5.85	24.38	14.63	5.85
MCC	21.44	15.59	9.74	15.59	9.74	2.92	15.59	9.74	2.92	15.59	9.74	2.92
Mg. Stearate	1.17	1.17	1.17	1.17	1.17	1.17	1.17	1.17	1.17	1.17	1.17	1.17
Talc	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78	0.78
Total	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00	80.00

Method of Preparation of mucoadhesive buccal tablets

Direct compression method was employed to prepare buccal tablets of Levosalbutamol sulphate using, chitosan, HPMC K4M as polymers. All the ingredients including drug, polymer and excipients were weighed accurately according to the batch formula (Table 1). The drug and all the ingredients except lubricants were taken on a butter paper with the help of a stainless steel spatula and the ingredients were mixed in the order of ascending weights and blended for 10 min in an inflated polyethylene pouch. After uniform mixing of ingredients, lubricant was added and again mixed for 2 min. The prepared blend of each formulation was pre-compressed by using different punches (6 mm) according to their weights on a single stroke tablet punching machine (Rimek Press Minipress II) at a pressure of 0.5 ton and turret speed of 2 rpm to form a buccal tablet.

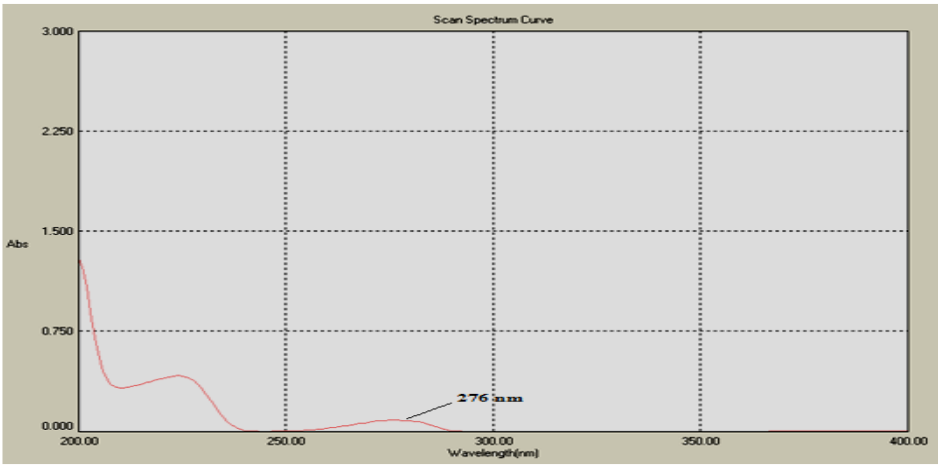
OBSERVATIONS AND RESULTS

Solubility

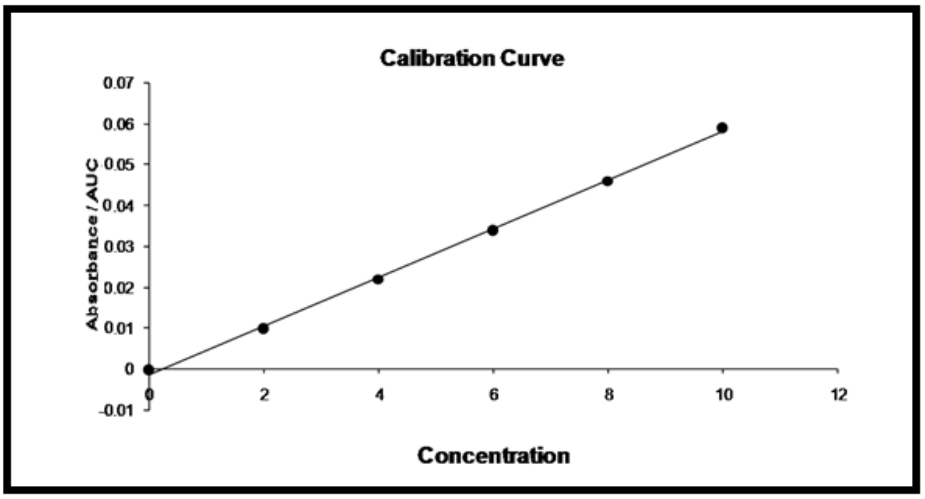
Table 2: Solubility of Levosalbutamol Sulphate in different solvents

Solvent	Solubility
Water	Freely soluble
Ethanol 95%	Slightly soluble
Ether	Slightly soluble
Dichloromethane	Very slightly soluble

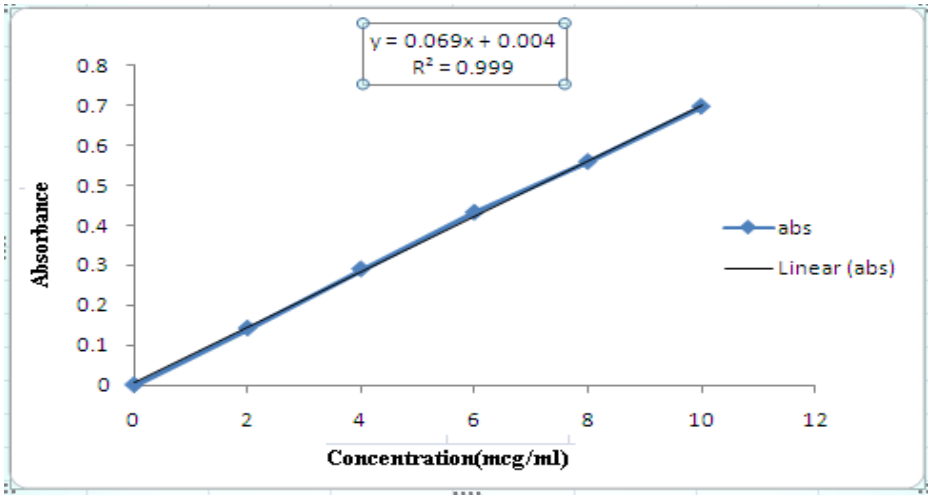
Melting point: 228^0 C



Graph 1: U.V. absorption spectrum of Levosalbutamol sulphate in Phosphate buffer (pH 6.8)



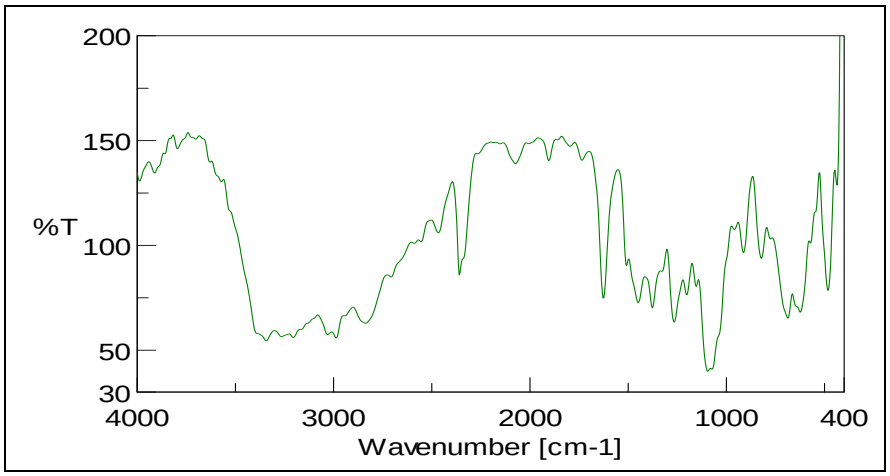
Graph 2: Calibration curve of Levosalbutamol Sulphate in distilled water



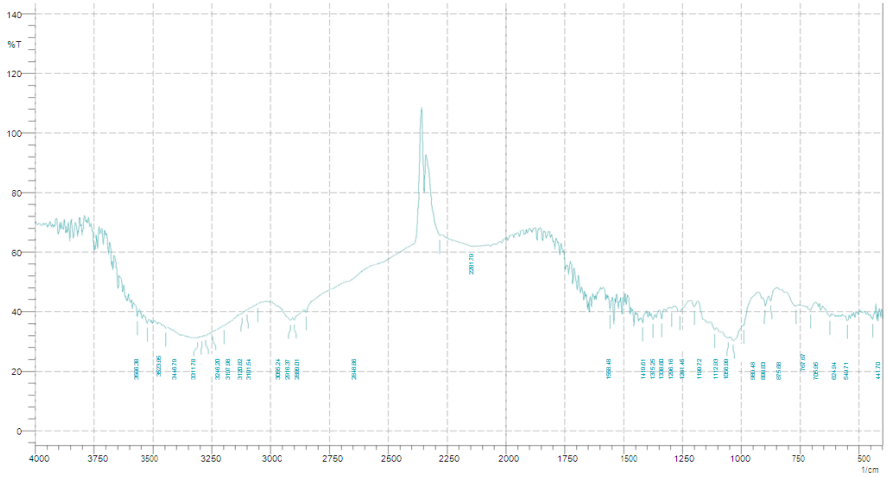
Graph 3: Calibration curve of Levosalbutamol Sulphate in phosphate buffer pH 6.8

Table no 3: Pre compression parameter for f1-f12.

Sr. no	Batch code	Bulk density	Tapped density	Carr's index	Hausner's ratio	Angle of repose
1	F1	0.75	0.81	7.40	1.08	32
2	F2	0.73	0.80	8.75	1.09	29
3	F3	0.75	0.82	8.53	1.09	31
4	F4	0.73	0.82	10.97	1.03	33
5	F5	0.70	0.77	9.09	1.05	31
6	F6	0.69	0.77	10.08	1.11	32
7	F7	0.69	0.78	10.04	1.02	31
8	F8	0.65	0.79	9.97	1.05	30
9	F9	0.74	0.78	10.02	1.06	29
10	F10	0.72	0.80	9.57	1.10	32
11	F11	0.68	0.81	9.79	1.04	31
12	F12	0.70	0.79	9.85	1.o1	30



Graph 4: FTIR spectra of Levosalbutamol Sulphate



Graph 5: FTIR spectra of Formulation of Levosalbutamol Sulphate

Table 4: Evaluation of post compressional parameters of mucoadhesive buccal tablets of Levosalbutamol Sulphate

Time (h)	Percentage weight change		
	F1	F2	F3
1	31.90±0.60	23.06±0.05	15.53±0.15
2	40.21±0.78	30.35±0.25	19.14±0.40
3	48.57±0.95	36.88±0.90	24.95±0.78
4	55.79±0.05	41.01±0.65	27.28±0.32
5	61.46±0.56	46.49±0.52	31.43±0.14
6	66.88±0.89	49.29±0.44	34.05±0.65
7	70.80±0.43	52.16±0.27	36.07±0.54
8	72.71±0.15	54.42±0.11	38.06±0.23

(n=3, Mean±SD)

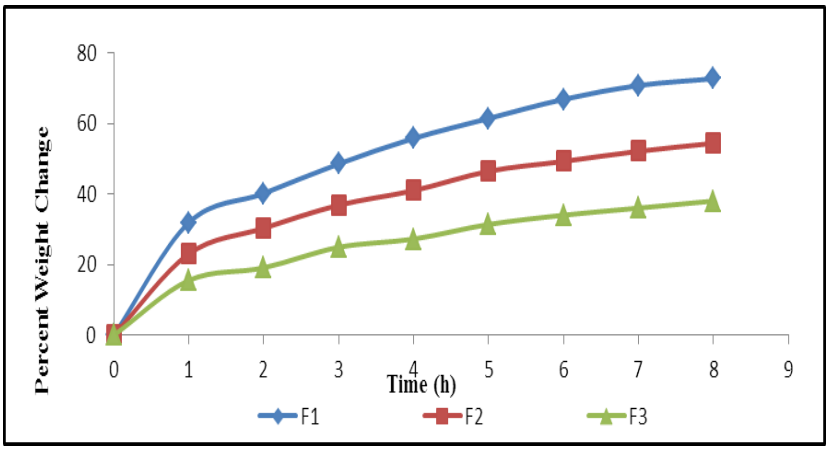
Table 5: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan (F1, F2 & F3)

Formulation code	Weight variation (mg)	Thickness (mm)	Diameter (mm)	Friability (%)	Hardness (kg/cm^2)	Disintegration Time (Min./Sec.)	Drug content (%)	Surface pH
F1	82	1	2.5	0.88	3	9	94	6.8
F2	82	2	2.4	0.85	3	10	93	6.7
F3	84	2	2.4	0.89	4	9	96	6.8
F4	86	2	2.6	0.85	4	9	98	6.8
F5	85	1	2.5	0.86	4	9	97	6.8
F6	83	2	2.5	0.85	3	9	97	6.8
F7	85	2	2.5	0.84	3	10	95	6.7
F8	85	2	2.4	0.88	4	8	93	6.6
F9	84	2	2.6	0.89	4	9	92	6.8
F10	82	2	2.6	0.87	4	9	98	6.5
F11	81	2	2.5	0.85	3	8	98	6.8
F12	83	2	2.5	0.86	3	9	94	6.8

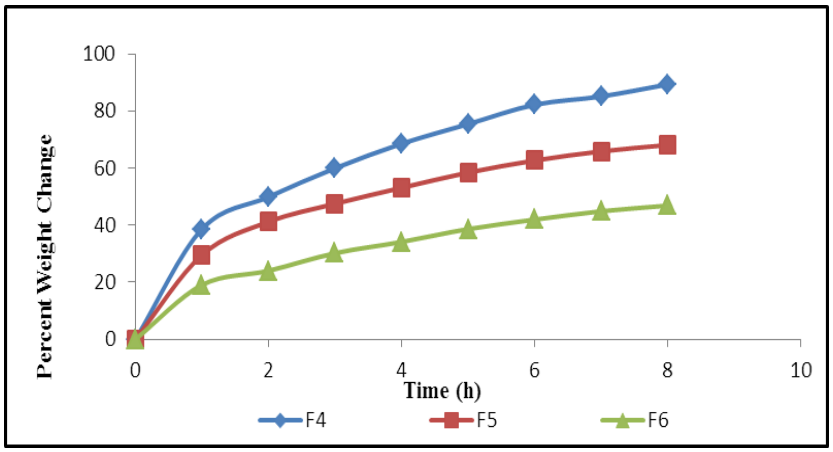
Table 6: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan and HPMC K4M (F4, F5 & F6)

Time (h)	Percentage weight change		
	F4	F5	F6
1	30.89±0.15	25.22±0.25	18.56±0.55
2	49.87±0.21	41.15±0.25	23.99±0.70
3	59.91±0.86	47.48±0.91	30.15±0.17
4	68.52±0.61	53.08±0.83	34.10±0.45
5	75.38±0.28	58.40±0.57	38.60±0.57
6	82.17±0.16	62.64±0.72	41.93±0.49
7	85.07±0.15	65.83±0.24	44.84±0.54
8	89.31±0.07	68.06±0.47	46.84±0.69

(n=3, Mean±SD)



Graph 6: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan (F1, F2 & F3)

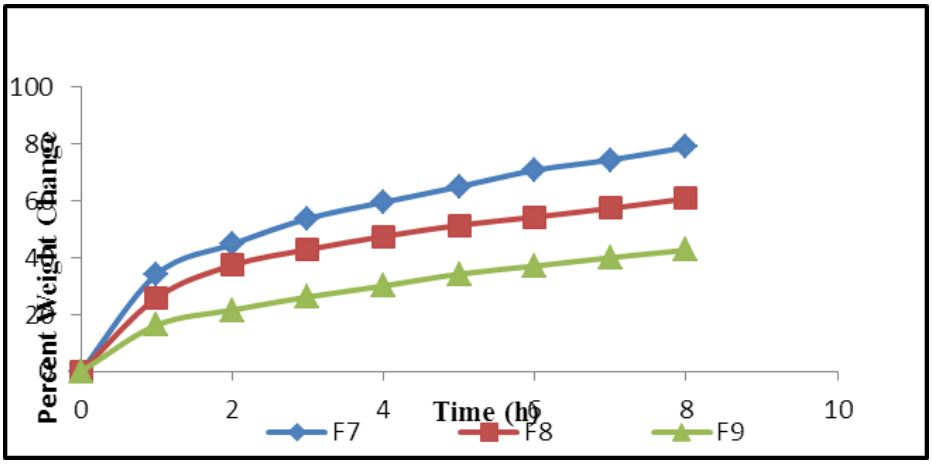


Graph 7: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan and HPMC K4M (F4, F5 & F6)

Table 7: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan and Xanthan gum (F7, F8 & F9)

Time (h)	Percentage weight change		
	F7	F8	F9
1	34.21±0.05	25.95±0.48	16.34±0.29
2	44.85±0.18	37.41±0.86	21.65±0.23
3	53.84±0.49	42.95±0.27	26.27±0.35
4	59.62±0.27	47.59±0.33	30.12±0.18
5	65.09±0.09	51.53±0.49	34.33±0.84
6	70.87±0.27	54.39±0.90	37.18±0.64
7	74.52±0.31	57.45±0.81	40.10±0.92
8	78.96±0.17	60.85±0.18	42.76±0.16

(n=3, Mean±SD)

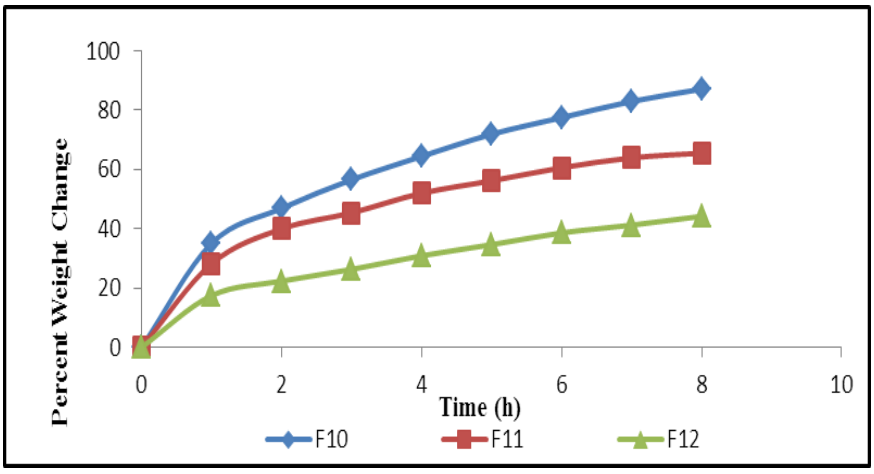


Graph 8: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan and xanthan gum (F7, F8 & F9)

Table 8: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan and Ethyl Cellulose (F10, F11 & F12)

Time (h)	Percentage weight change		
	F10	F11	F12
1	35.07±0.09	28.21±0.19	17.47±0.42
2	46.89±0.18	39.95±0.27	22.37±0.82
3	56.52±0.28	45.37±0.57	26.30±0.67
4	64.39±0.40	51.98±0.34	30.91±0.27
5	71.85±0.34	56.18±0.41	34.65±0.68
6	77.48±0.29	60.57±0.61	38.61±0.53
7	82.92±0.69	63.92±0.85	41.23±0.26
8	87.08±0.46	65.50±0.72	44.20±0.19

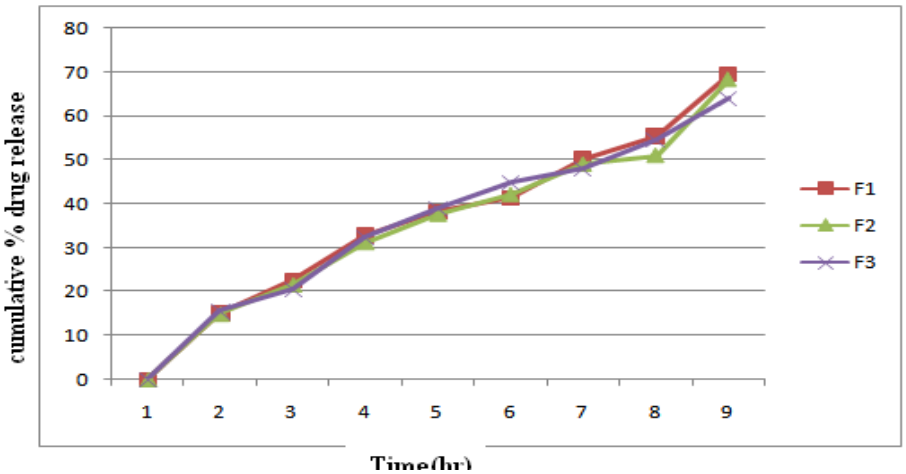
(n=3, Mean±SD)



Graph 9: Swelling data of mucoadhesive buccal tablets of Levosalbutamol Sulphate containing chitosan and Ethyl Cellulose (F10, F11 & F12)

Table 09: *In-vitro* release data of Levosalbutamol Sulphate from mucoadhesive buccal tablets containing chitosan (F1, F2 & F3)

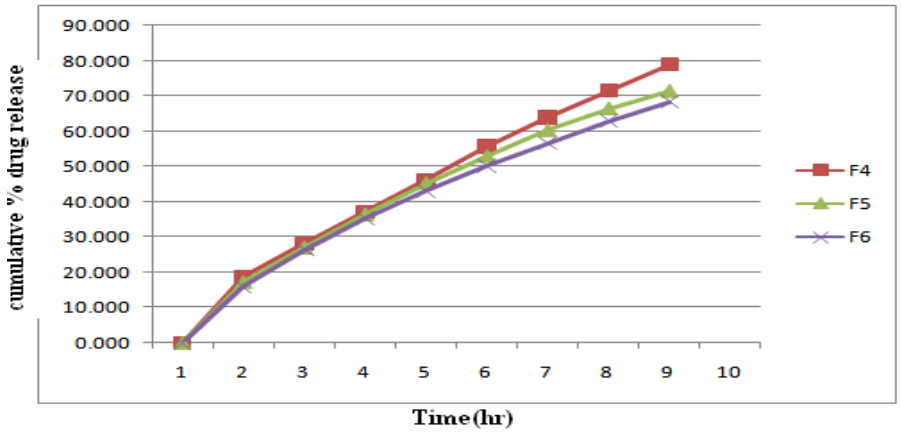
Time (h)	*In vitro* release		
	F1	F2	F3
0	0.00	0.00	0.00
1	15.12	14.88	15.48
2	22.63	21.60	20.55
3	32.75	31.22	32.25
4	38.21	37.72	39.07
5	41.35	42.21	44.86
6	50.40	49.08	48.12
7	55.39	51.10	54.55
8	69.43	68.39	63.99



Graph 10: *In-vitro* drug release profiles of formulation F1-F3

Table10: *In-vitro* release data of Levosalbutamol sulphate from mucoadhesive buccal tablets containing chitosan and HPMC K4M (F4, F5 & F6)

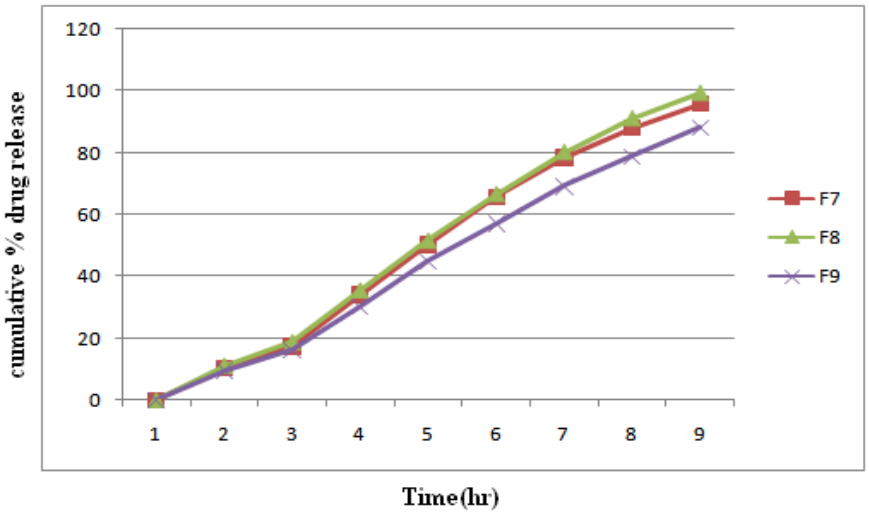
Time (h)	*In vitro* release		
	F4	F5	F6
0	0.00	0.00	0.00
1	18.77	17.32	16.04
2	28.07	27.05	26.42
3	37.09	36.45	35.22
4	46.12	45.32	43.06
5	55.58	53.03	50.09
6	63.82	60.33	56.59
7	71.32	66.49	62.71
8	78.78	71.44	68.15



Graph 11: *In-vitro* drug release profiles of formulation F4-F6

Table 11: *In-vitro* release data of Levosalbutamol Sulphate from mucoadhesive buccal tablets containing chitosan and xanthan gum (F7, F8 & F9)

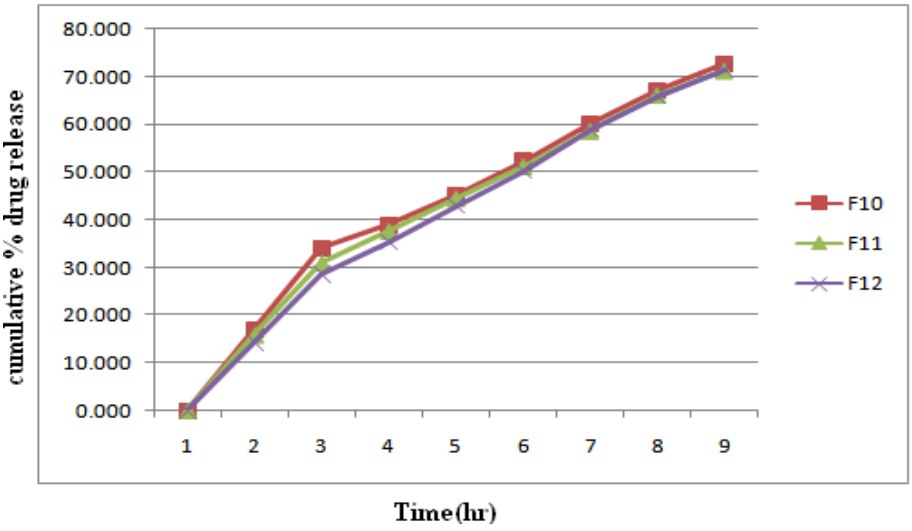
Time (h)	*In vitro* release		
	F7	F8	F9
0	0.00	0.00	0.00
1	10.35	11.14	9.58
2	17.43	18.71	15.98
3	34.14	35.42	30.41
4	50.24	51.47	44.94
5	65.79	66.57	57.13
6	78.38	80.09	69.19
7	88.12	91.01	79.01
8	95.83	99.24	88.22



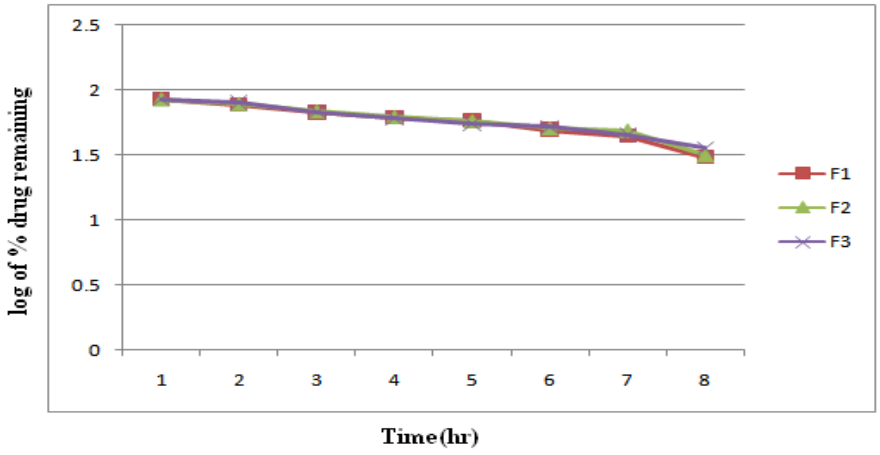
Graph 12: *In-vitro* drug release profiles of formulation F7-F9

Table 12: *In-vitro* release data of Levosalbutamol sulphate from mucoadhesive buccal tablets containing chitosan and Ethyl Cellulose (F10-F12)

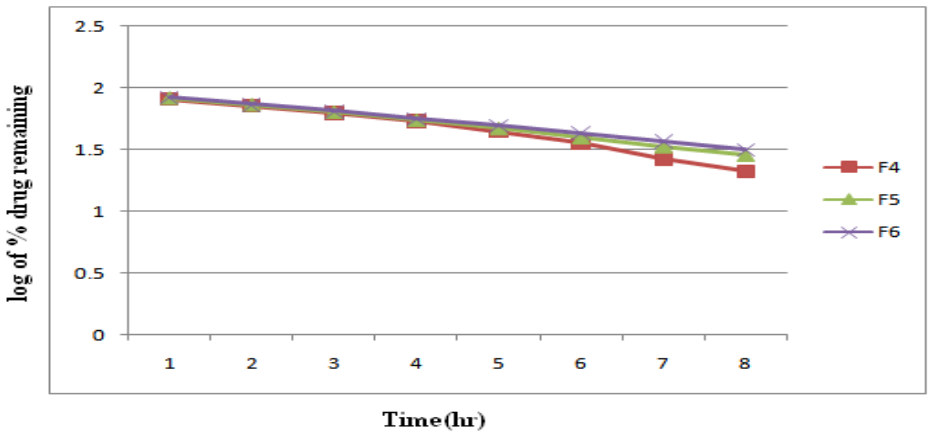
Time (h)	*In vitro* release		
	F10	F11	F12
0	0.00	0.00	0.00
1	17.00	15.88	14.43
2	34.05	31.04	28.66
3	39.07	37.65	35.36
4	45.06	44.48	43.05
5	52.35	51.18	50.28
6	60.28	58.59	59.03
7	67.10	66.17	65.93
8	72.72	71.25	71.55



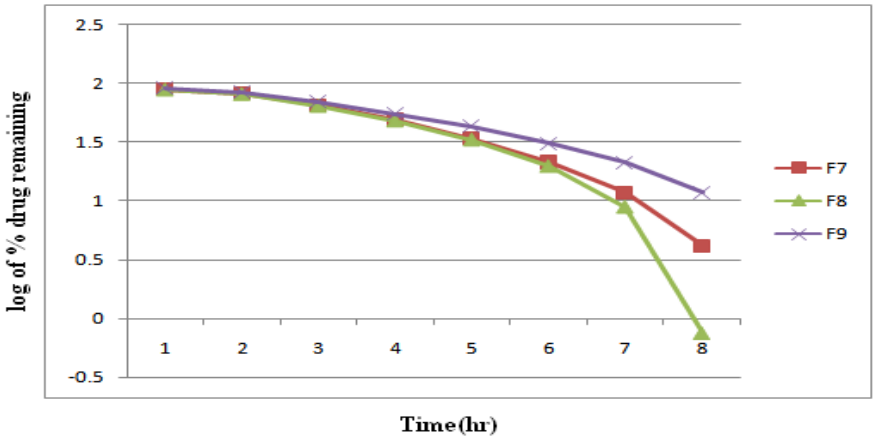
Graph 13: *In-vitro* drug release profiles of formulation F10-F12



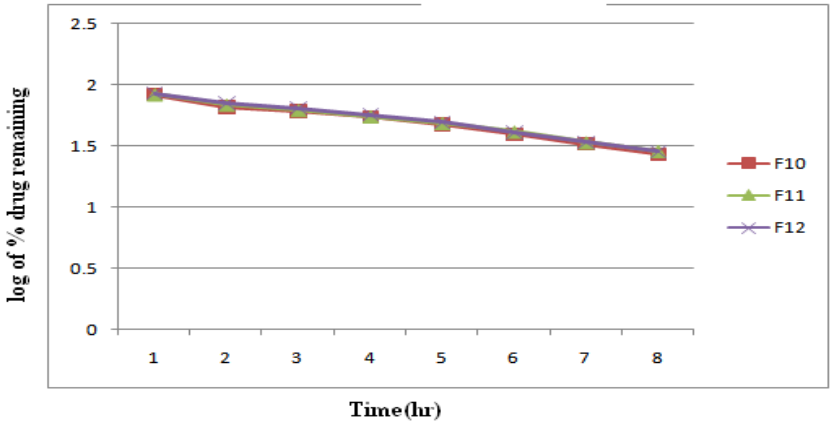
Graph 14: Log cumulative % drug remaining Vs time plots (First order) of formulations F1-F3



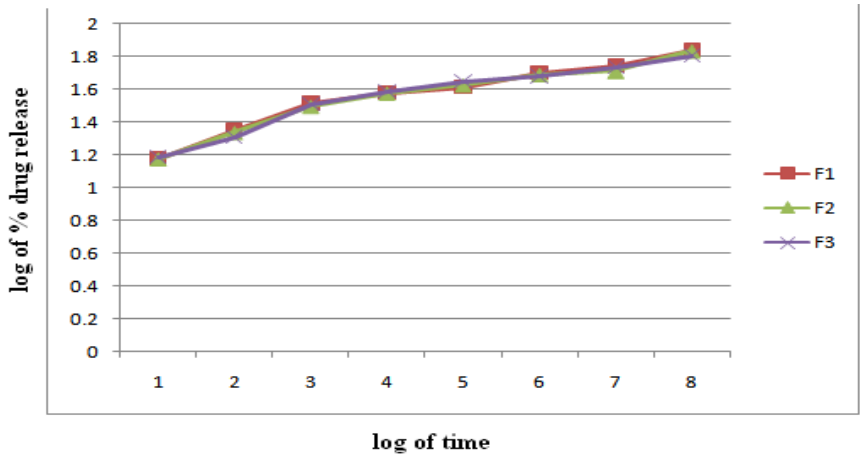
Graph 15: Log cumulative % drug remaining Vs time plots (First order) of formulations F4-F6



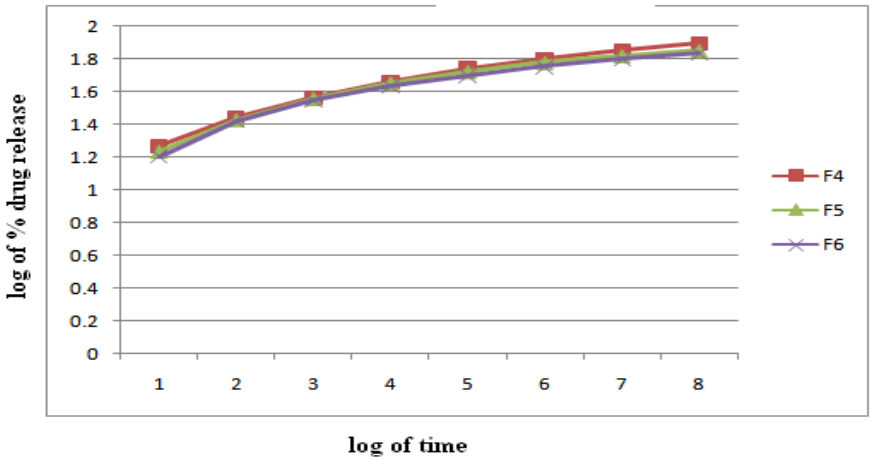
Graph 16: Log cumulative % drug remaining Vs time plots (First order) of formulations F7-F9



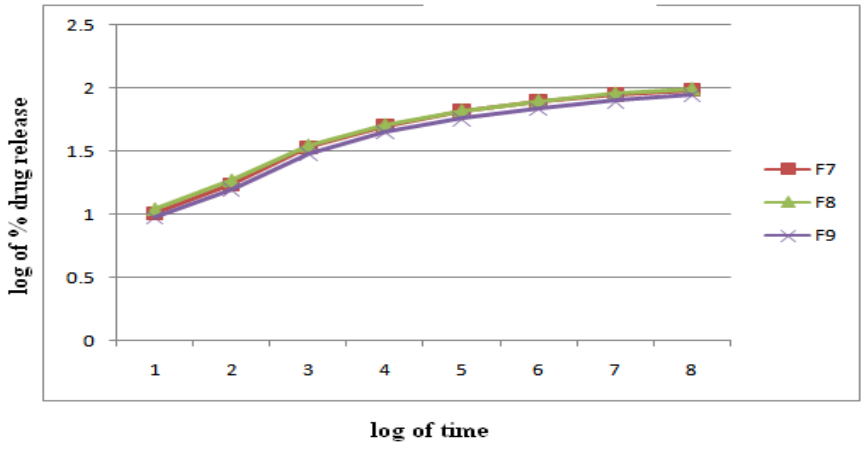
Graph 17: Log cumulative % drug remaining Vs time plots (First order) of formulations F10- F12



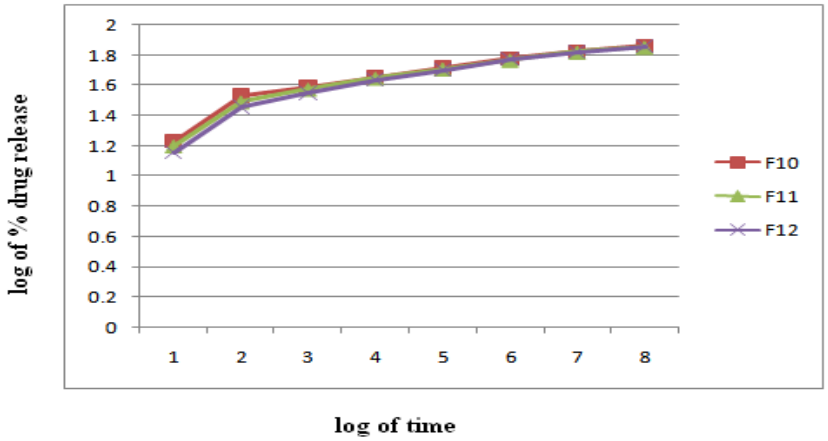
Graph 18: Log cumulative % drug release Vs log of time plots (Korsmeyer-Peppas) of formulations F1, F2, & F3



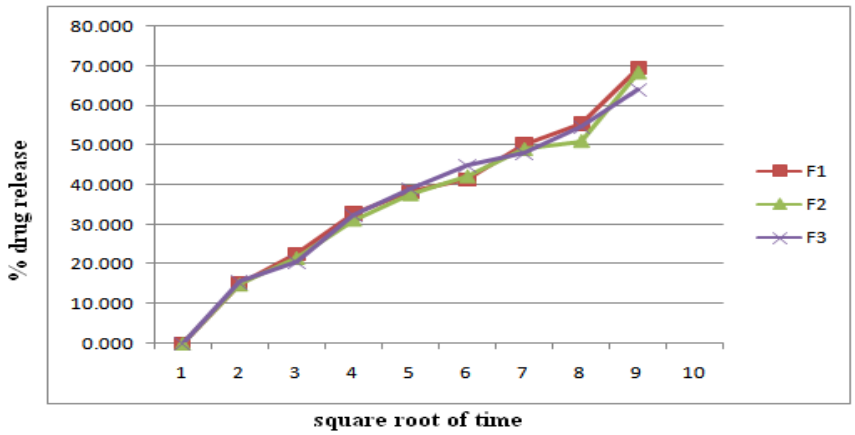
Graph 19: Log cumulative % drug release Vs log of time plots (Korsmeyer-Peppas) of formulations F4, F5, & F6



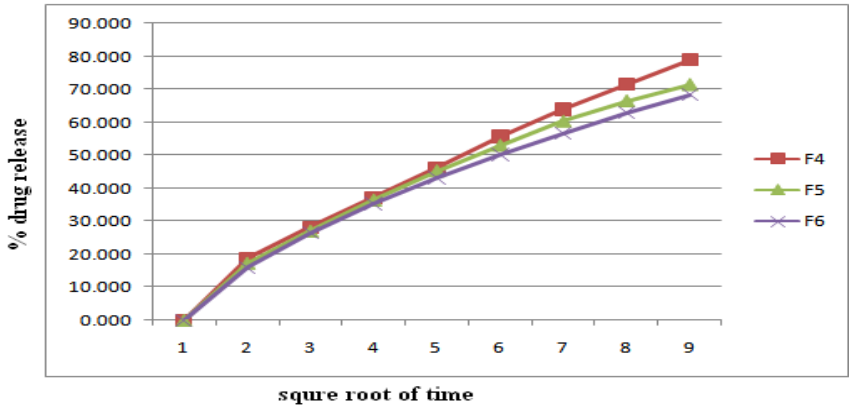
Graph 20: Log cumulative % drug release Vs log of time plots (Korsmeyer-Peppas) of formulations F7, F8, & F9



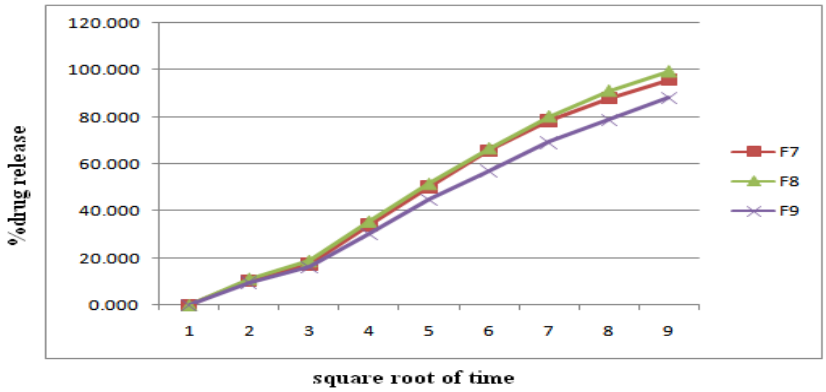
Graph 21: Log cumulative % drug release Vs log of time plots (Korsmeyer-Peppas) of formulations F10, F11, & F12



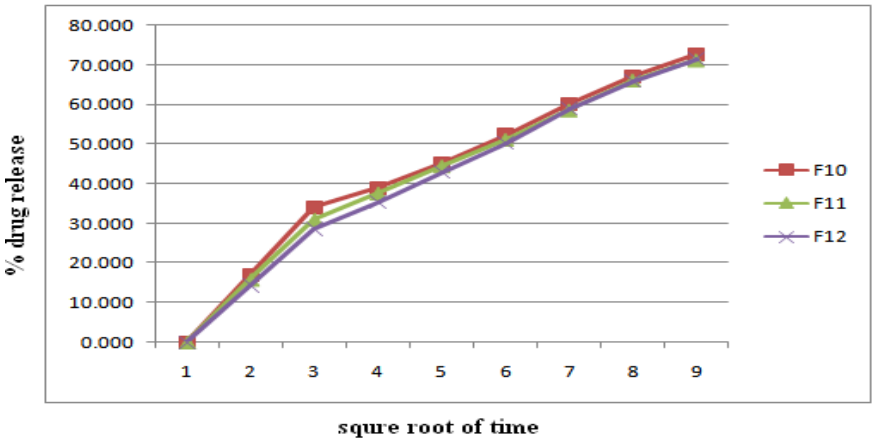
Graph 22: Log cumulative % drug release Vs square root of time plots (Higuchi) of formulations F1, F2, & F3



Graph 23: Log cumulative % drug release Vs square root of time plots (Higuchi) of formulations F4, F5, & F6



Graph 24: Log cumulative % drug release Vs square root of time plots (Higuchi) of formulations F7, F8, & F9



Graph 25: Log cumulative % drug release Vs square root of time plots (Higuchi) of formulations F10, F11, & F12

Table 13: Regressional analysis of the *in-vitro* release data according to various release kinetic models

Formulation code	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer-Peppas r^2
F1	0.976	0.932	0.976	0.908
F2	0.968	0.914	0.946	0.936
F3	0.973	0.977	0.968	0.924
F4	0.974	0.977	0.981	0.946
F5	0.974	0.997	0.979	0.917
F6	0.973	0.998	0.981	0.908
F7	0.990	0.909	0.900	0.901
F8	0.992	0.982	0.975	0.908
F9	0.994	0.946	0.955	0.913
F10	0.957	0.985	0.983	0.987
F11	0.966	0.990	0.981	0.956
F12	0.978	0.991	0.972	0.945

DISCUSSION

Levosalbutamol sulphate is $5HT_1$ receptor agonist with low oral bioavailability due to extensive first pass metabolism. We have tried to prepare mucoadhesive drug delivery system using Levosalbutamol as a drug and chitosan, HPMC as a mucoadhesive and release retardant polymers over a period of 8 hours which bypasses first pass metabolism and may enhance bioavailability.

The FTIR spectra of drug alone and with the excipients obtained is illustrated in graph 4 and 5 reveals that Levosalbutamol sulphate was in the free form and no drug-polymer and polymer-polymer interactions took place during formulation development.

Precompressional Parameters were evaluated for bulk density, tapped density, Carr's index, Hausner's ratio and angle of repose. Results were represented in Table 3. Postcompressional parameters were studied and represented in Table 4. The drug content was from 97.95% to 103.36% suggested uniform mixing of drug. The surface pH for all the buccal tablets was from 6.68 to 7.04 which were nearer to salivary pH (6.5-7.5) suggesting that the prepared buccal tablets can be used without the risk of mucosal irritation and discomfort.

The swelling study of prepared buccal tablets was performed in phosphate buffer pH 6.8 and the results are presented as percentage weight change with respect to time in Table 5-8and in graph 6-9. The swelling of all the tablets was increased as the time proceeds because the polymer gradually absorbs water due to hydrophilicity of the polymer. The swelling index was 38.06% to 89.31% for the formulation which contains ethyl cellulose with chitosan. As the concentration of chitosan increased alone and in combination of secondary polymers, the swelling was decreased because of more viscous layer formation.

The *in vitro* release of Levosalbutamol sulphate was also depends on swelling behaviour of the polymers used. The buccal tablets containing chitosan with ethyl cellulose showed prolonged release of Levosalbutamol sulphate from 6 to 8 h. The buccal tablets containing chitosan with Xanthan gum showed a maximum release of 88.22% to 99.24% after 8 hours.

The in vitro release data was represented in Table 9-12 and illustrated in graph 10-13. The in vitro release of Levosalbutamol sulphate was also depends on swelling behaviour of the polymers used. The buccal tablets containing chitosan alone showed initially a rapid burst release of the drug followed by > 90% release within 4 h.

The in vitro release data was subjected to zero order, first order, Higuchi, Korsmeyer-Peppas, Hixson Crowell and erosion model in order to establish the drug release mechanism and kinetics of drug release from the buccal tablets in Table 13 and illustrated in graph 14-25. In all cases the release of Levosalbutamol followed mixed release kinetics where Zero order release kinetics was predominant.

CONCLUSION

The study suggests that the mucoadhesive tablet of Levosalbutamol sulphate using natural and synthetic polymers regulated the release up to 8 hrs. The tablet demonstrated the post compressional parameters within the range with residence time of 8 hours and swelling index of the tablet enhanced slowly with increased amount of chitosan and Xanthan gum in combination. Formulation F8 was found to be the promising formulation to achieve the aim of this study showing highest drug release and which may result in improved bioavailability.

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